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**SYNTHETIC STUDIES ON THE PEDERIN FAMILY OF ANTITUMOUR AGENTS.
SYNTHESES OF PEDERIN, MYCALAMIDE B AND ANALOGUES**

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PhD

Department of Chemistry

September, 2000



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ABSTRACT

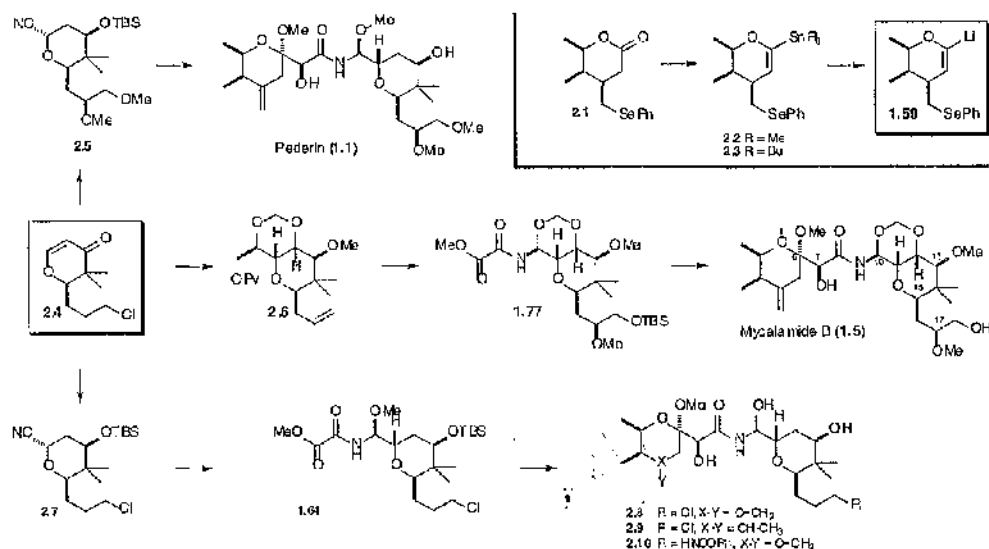
FACULTY OF SCIENCE

Doctor of Philosophy

SYNTHETIC STUDIES ON THE PEDERIN FAMILY OF ANTITUMOUR AGENTS. SYNTHESES OF PEDERIN, MYCALAMIDE B AND ANALOGUES

by Robert Narquizian

A general modular approach to members of the pederin family of antitumour agents, exemplified by syntheses of pederin (**1.1**), mycalamide B (**1.5**) and analogues (**17-epi-1.5**, **2.8**, **2.9** and **2.10**), is described. The common strategy makes use of a metallated dihydropyran approach to couple two advanced fragments. All 6 compounds are prepared from 6-lithio-2,3-dimethyl-4-phenylselenomethyl-3,4-dihydro-2*H*-pyran **1.59** and 2-(3-chloropropyl)-3,3-dimethyl-3,4-dihydro-2*H*-pyran-4-one **2.4**. The key steps in the synthesis of pederin **1.1** or its analogues are Sharpless asymmetric dihydroxylations and a rhodium-catalysed directed reduction of an acylimidate. The key steps in the synthesis of the right fragment of mycalamide B **1.5** are a P_2O_5 -mediated formation of the trioxadecalin ring, a Meerwein-Ponndorf-Verley reduction to install the C13-stereogenic centre, installation of the C10-N bond in good yield and total stereocontrol at the C10 centre *via* a Curtius rearrangement and/or a Hofmann rearrangement, as well as Sharpless asymmetric dihydroxylations.



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Preface

The research described in this thesis was carried out under the supervision of Professor P. J. Kocienski at the University of Glasgow between October 1997 and September 2000.

Part of this thesis has been previously published :

- P. J. Kocienski, R. Narquizian, P. Raubo, C. Smith, and F. T. Boyle, *Synlett*, **1998**, 869.
- P. J. Kocienski, R. Narquizian, P. Raubo, C. Smith, and F. T. Boyle, *Synlett*, **1998**, 1432.
- P. J. Kocienski, R. Narquizian, C. Raubo, C. Smith, L. F. Farrugia, and K. Muir, *J. Chem. Soc., Perkin Trans. 1*, **2000**, 2357.
- R. Narquizian, P.J. Kocienski, "The Pederin Family of Antitumour Agents: Structures, Synthesis and Biological Activity", in proceeding of the Ernst Schering Foundation Workshop on "Drugs from Natural Products", Springer Verlag, Berlin, **2000**, Chapter 2, *in press*.

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I gratefully acknowledge the University of Glasgow for financial support.

Last but not least, I would like to thank all my family for their every moments encouragements.

Abbreviations

Å	angstrom
Ac	acetyl
AD	asymmetric dihydroxylation
AIBN	2,2'-azobis(2-methylpropionitrile)
Allyl	2-propenyl
Anal.	combustion analysis
aq	aqueous
Ar	aryl
BINAP	1,1'-bis(diphenylphosphino)-1,1'-binaphthyl
Bn	benzyl
bp	boiling point
ⁿ BuLi	<i>n</i> -butyllithium
<i>c</i>	concentration in g/100 mL (for optical rotation)
COSY	correlation spectroscopy
CSA	camphorsulfonic acid
CI	chemical ionisation
d	days
D	dextro rotary
Δ	reflux
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]undecene-7
de	diastereomeric excess
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DHQ	dihydroquinine
DHQD	dihydroquinidine
DIAD	<i>diiso</i> -propyl azodicarboxylate
DIBAL	<i>diiso</i> -butylaluminium hydride
DIPEA	<i>diiso</i> -propylethylamine
DMAP	4-dimethylaminopyridine
DMF	<i>N,N'</i> -dimethylformamide
DMPM	dimethoxyphenylmethyl
DMPU	1,3-dimethyl-3,4,5-tetrahydro-2(1 <i>H</i>)-pyrimidinone

DMS	dimethyl sulfide
DMSO	dimethyl sulfoxide
dr	diastereomeric ratio
er	enantiomeric ratio
EI	electron impact
eq	equivalents
ES	electrospray
Et	ethyl
FAB	fast atom bombardment
g	gram
h	hours
HMBC	heteronuclear multiple quantum coherence
HMPA	hexamethylphosphoramide
HMQC	heteronuclear multiple bond correlation
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
i	<i>iso</i>
IC	inhibition constant
Im	imidazole
i.p.	intra peritoneal
IR	infrared
Kg	kilogram
KHMDS	potassium hexamethyldisilazide
L	levo rotary
LAH	lithium aluminium hydride
LDA	lithium di <i>iso</i> -propylamide
LRMS	low resolution mass spectrometry
M	molarity
<i>m</i> CPBA	<i>meta</i> -chloroperbenzoic acid
Me	methyl
MEM	methoxyethoxymethyl
mg	milligram
MHz	megahertz
MIC	minimum inhibitory concentration
min	minute
ml	millilitre
mmol	millimole
MOM	methoxymethyl
mp	melting point

Ms	methanesulfonyl
MS	molecular sieves
MTPA	α -methoxy- α -(trifluoromethyl)phenylacetic acid
n	normal
ng	nanogram
nM	nanomolar
NMR	nuclear magnetic resonance
NOe	nuclear Overhauser effect
PDC	pyridinium dichromate
Ph	phenyl
Pv	pivaloyl
ppm	parts per million
PPTS	pyridinium <i>para</i> -toluenesulfonate
Pr	propyl
py	pyridine
rt	room temperature
s	secondary
SAR	structure activity relationship
SEM	2-(trimethylsilyl)ethoxymethyl
t	tertiary
TBAF	tetrabutylammonium fluoride
TBS	<i>tert</i> -butyldimethylsilyl
TBSCN	<i>tert</i> -butyldimethylsilyl cyanide
TBSOTf	<i>tert</i> -butyldimethylsilyl triflate
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy
THF	tetrahydrofuran
TLC	thin layer chromatography
TMEDA	<i>N, N, N', N'</i> -tetramethylethylenediamine
TMS	trimethylsilyl
TPAP	tertrapropylammonium perruthenate
Tr	trityl
Ts	<i>para</i> -toluenesulfonyl
UV	ultraviolet

The Pederin Family of Antitumour Agents: Structures, Synthesis and Biological Activity

1. INTRODUCTION

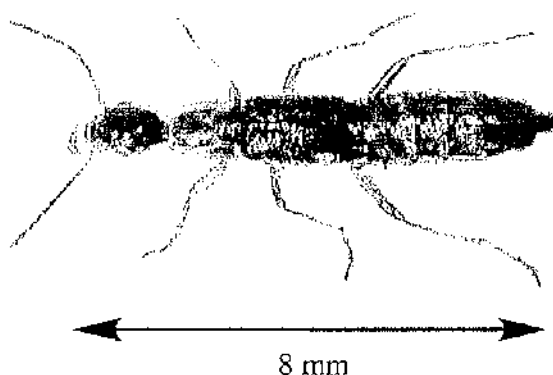
1.1 Structures

In 1775 the Danish entomologist Johann Christian Fabricius (1745-1808) first described the genus *Paederus* which at that time included only two species. In the ensuing two centuries, over 600 species have been identified including *Paederus fuscipes* whose natural history deserves some mention.¹ *Paederus fuscipes* (picture 1.1) is about 8 mm long with a black head and abdominal apex, an orange thorax and abdominal base and iridescent blue elytra (wing case). It inhabits riverbanks, marshes, and irrigated fields where it feeds mainly on insects, mites, soil nematodes, and decaying vegetable matter. Like most members of the genus, *Paederus fuscipes* is a predator of the fly population but it is also a pest to man. The insect doesn't sting or bite but a toxin in its hemolymph causes severe dermatitis when it is crushed on the skin and the eyes are particularly sensitive though the palms of the hand and the soles of the feet are resistant. In addition to the lesions, severe symptoms such as fever, oedema, neuralgia, arthralgia, and vomiting are observed with erythema persisting for several months. It has been suggested¹ that both the affliction and its causative agent were known to Chinese medicine over 1200 years earlier. An insect called *ch'ing yao ch'ung* was described in A. D. 739 by Ch'en : "it contains a strong poison and when it touches the skin it causes the skin to swell up. It will take the skin off one's face and remove tattoo marks completely. It is used as a caustic for toxic boils, nasal polypi, and ringworm."

The active chemical agent responsible for the dermatitis was first isolated in crystalline form by Nctolitzky in 1919.²⁻⁴ The research which eventually led to the correct structure began in 1952 with Pavan and Bo⁵ who named the toxic agent pederin and determined its melting point (112°C) on a sample derived from 25 million specimens (ca 100 kg). The correct molecular formula (C₂₅H₄₅O₉N) established by Quilico⁶ in 1961 led to detailed study of the chemical constitution of pederin and a structure, devoid of stereochemical definition, was proposed in 1965.⁷ An independent investigation by Matsumoto's team at Sapporo gave corroborating evidence.^{8,9} With one minor exception (*vide infra*) all the conclusions drawn from the degradation and ¹H NMR studies of Quilico¹⁰ and Matsumoto were later confirmed by an X-ray crystallographic analysis of pederin di-*p*-bromobenzoate^{11, 12} which also established the absolute and relative stereochemistry.

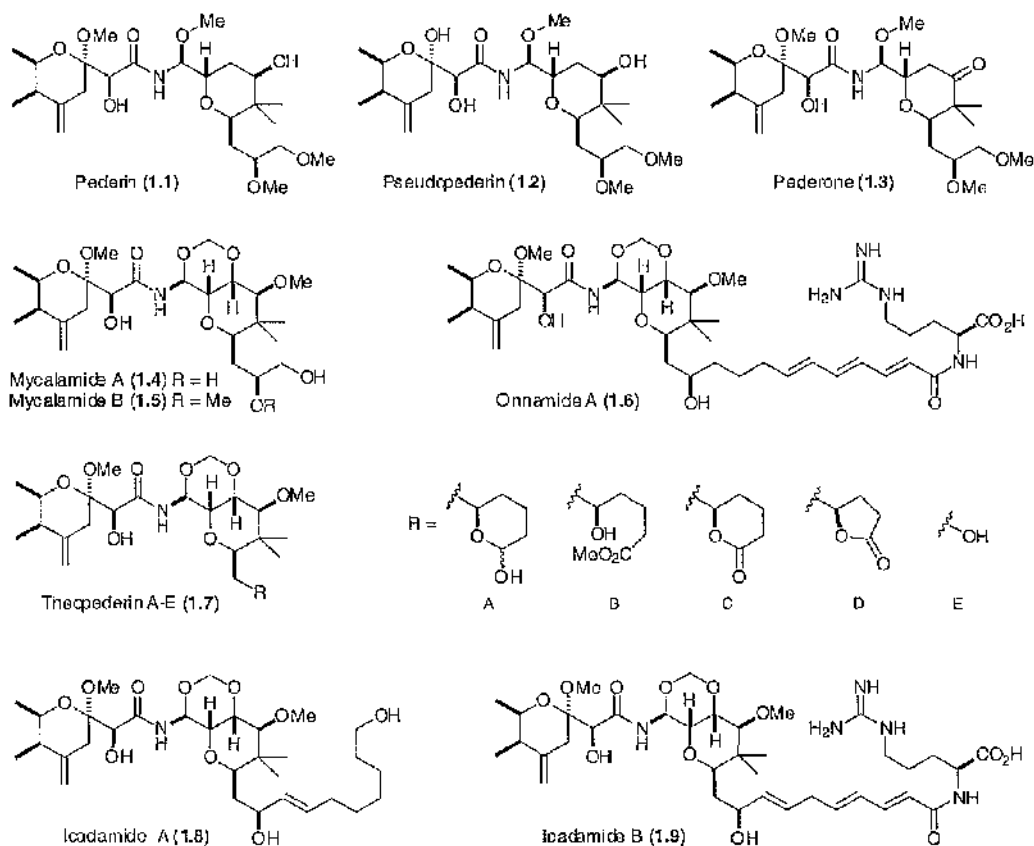
Single *Paederus riparius* specimens reared from the egg and kept for prolonged periods of time show that only the females are able to biosynthesise pederin.¹³⁻¹⁵ Preimaginal stages efficiently store pederin transferred by the females into their eggs and the males' pederin content decreases slowly over time. Only males with access to eggs containing the substance moderately increase their pederin load. The females begin to accumulate the toxin a few weeks after imaginal eclosion and build up reserves for the egg laying period within 60 days.

Paederus fuscipes



Picture 1.1

For many years, pederin (**1.1**), pseudopederin (**1.2**)⁷ and pederone (**1.3**)¹⁶ (also isolated from *Paederus fuscipes*) were structurally unique in the realm of natural products. However, in 1988 routine screening for antiviral agents identified two marine natural products which bore a close structural resemblance to pederin. Mycalamide A (**1.4**) was isolated from a sponge of the genus *Mycale* found in the Otago harbour off New Zealand^{17, 18} whilst onnamide A (**1.6**) was isolated from a sponge of the genus *Theonella* found in Okinawan waters¹⁹. The pederin family grew to 24 members by 1995 with the isolation of mycalamide B (**1.5**)¹⁸, a further 11 onnamides^{20, 21} and theopederins A-E (**1.7**)²². The most recent additions to the pederin family are icadamides A (**1.8**) and B (**1.9**) isolated from a sponge of the genus *Leiosella*.²³ The significance of the mycalamides, onnamides, theopederins and icadamides in sponge physiology is unclear although it has been suggested that the occurrence of closely related compounds in such taxonomically remote animals as sponges and terrestrial beetles may indicate connection by a common producer, possibly a symbiotic micro-organism.²⁴

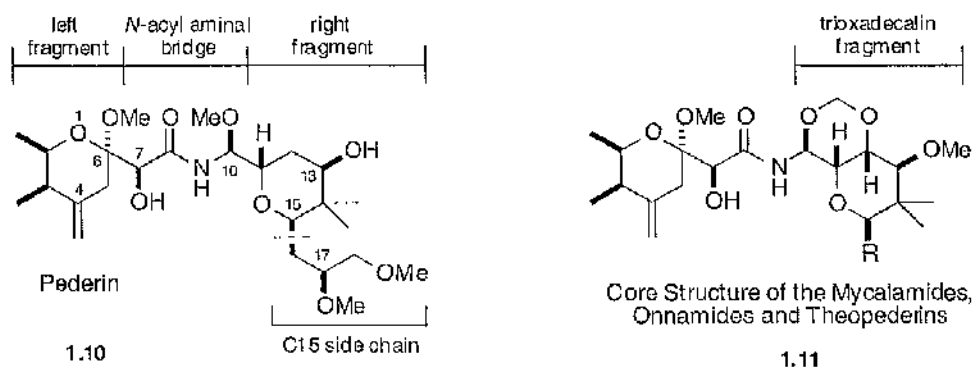


Scheme 1.1

1.2. Synthetic Studies

All members of the pederin family are rare, difficult to isolate, and comparatively frail; many of them have potent and potentially useful activity as antiviral and antitumour agents (see below) which has stimulated considerable interest in their total synthesis. Total syntheses of pederin²⁵⁻³³, mycalamide A³⁴⁻³⁷, mycalamide B^{34, 38}, onnamide A³⁹ and theopederin D³³ have been reported as have significant syntheses of various fragments^{35, 40-56}. The parent member of the family, pederin itself, is also the simplest. It is composed of two tetrahydropyran rings (a left fragment and a right fragment) connected by an *N*-acyl aминаl bridge as depicted in structure **1.10** (Scheme 1.2). The left fragment of all members of the pederin family is identical but all remaining members of the family (the mycalamides, onnamides, theopederins and icadamides) have a trioxadecalin right fragment as shown in structure **1.11**. The principal site of structural variation is the side chain attached to C15. The common left fragment also imposes a common problem: the high acid lability associated with the alkene at C4 which activates the acetal function at C6. A comprehensive discussion of the syntheses of members of the pederin family is beyond the scope of this review so we will focus on one of the most demanding challenges: the

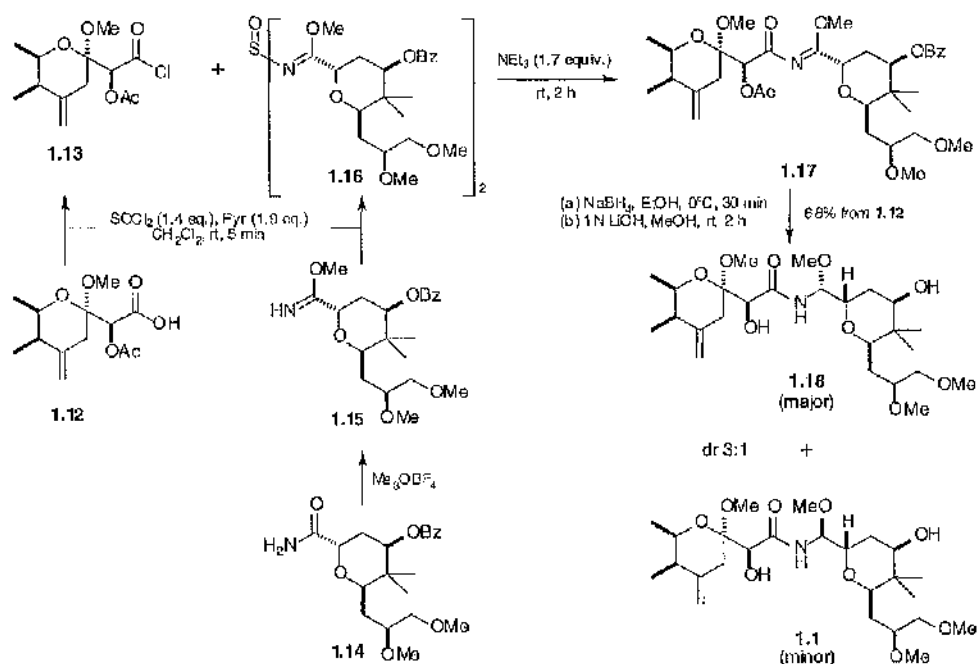
construction of the *N*-acyl aminal bridge linking the left and right fragments. The following discussion is arranged according to the bond formed in the fragment linkage strategy.



Scheme 1.2

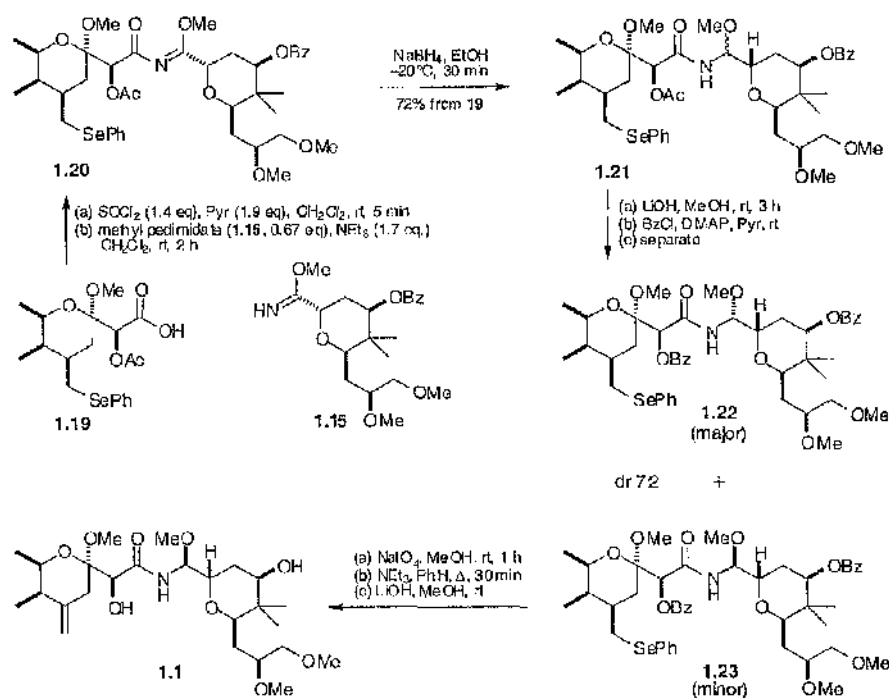
1.2.1. The C8–N9 Connection via Imidate Ester Acylation

Matsumoto and his team reported the first total synthesis of pederin in 1982 in which the left and right fragments were connected by the *N*-acylation of an imidate ester (Scheme 1.3).^{25, 57} The crucial coupling reaction was accomplished by *brief* treatment of (+)-acetylpederic acid (**1.12**) with thionyl chloride in the presence of pyridine in dichloromethane followed by addition of methyl pedimide (**1.15**). The reaction time had to be minimised owing to the instability of the acid chloride intermediate **1.13**. Unfortunately, the highly hindered carboxylic acid was converted slowly to the acid chloride **1.13** under the reaction conditions thereby allowing time for the reaction of imidate ester **1.15** with thionyl chloride to give *N,N'*-sulfinyl-bis(methyl pedimide) (**1.16**) which can also serve as a substrate in the acylation of acid chloride **1.13**. Thus, the formation of *N*-acyl imidate intermediate **1.17** occurred by two different paths concurrently. The *N*-acyl aminal bridge was then constructed by reduction of **1.17** with sodium borohydride. The synthesis was completed by hydrolysis of the benzoate and acetate ester protecting groups to give a mixture of pederin (**1.1**) and 10-*epi*-pederin (**1.18**) in a ratio of 1:3 [68% overall from (+)-benzoylpedamide (**1.14**)] with pederin being the minor product.



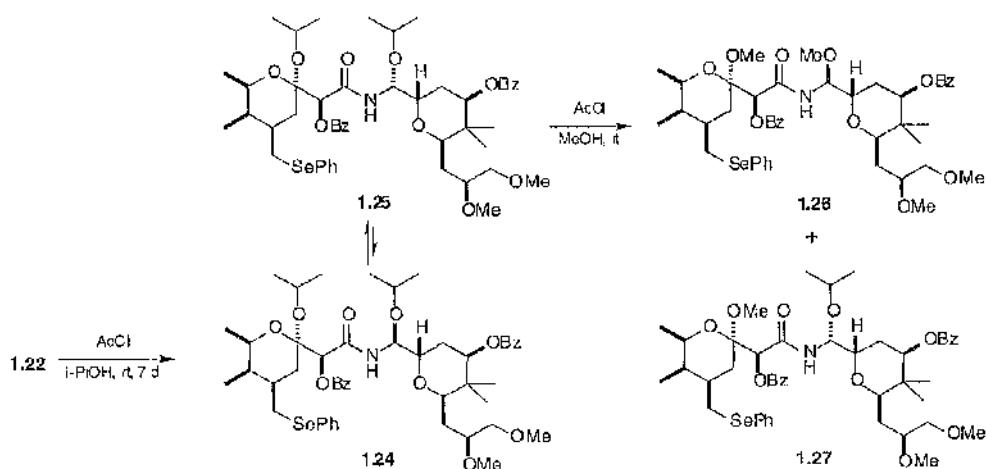
Scheme 1.3

The high acid sensitivity of the homoallylic acetal in (+)-acetylpederic acid (**1.12**) was a major obstacle to Matsumoto's first synthesis. In a subsequent refinement, the C4 alkene was carried through the synthesis in latent form with the troublesome alkene being introduced in the penultimate step of the synthesis as shown in Scheme 1.4.²⁶ However, the reduction of *N*-acyl imide **1.20** once again afforded an unfavourable mixture of *N*-acyl aminals **1.21** in 72% overall yield (dr 7:2). After chromatographic separation, the requisite alkene was introduced by brief thermolysis of the selenoxide derived from oxidation of the minor selenoether **1.23** whereupon hydrolysis of the C7 and C13 benzoates afforded pederin (**1.1**).



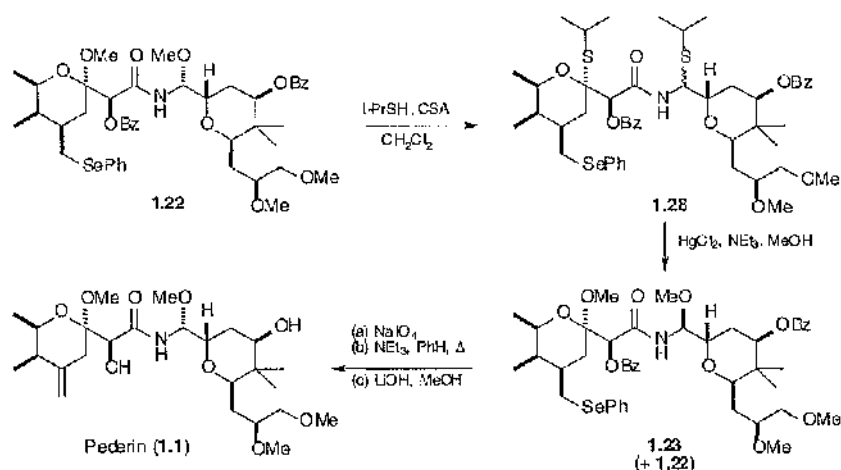
Scheme 1.4

The poor stereoselectivity in the reduction of the *N*-acyl imidates **1.17** and **1.20** in the foregoing studies was beyond repair and so isomerisation of the *N*-acyl aminal in the 10-*epi*-pederin series was investigated. Transacetalisation of 10-*epi*-pederin derivative **1.22** with acetyl chloride in methanol (rt, 3 h) gave an equilibrium mixture (**1.22**:**1.23** = 3:1) showing that the undesired 10-*epi* series was the thermodynamic product. The possibility of selective conversion of the 10-*epi*-pederin derivative **1.22** into pederin derivative **1.23** under *kinetically* controlled conditions was next examined, by taking into account the acceleration effect of the alkoxy-exchange reaction in methanol by a large alkoxy group.³⁰ Thus, treatment of **1.22** with acetyl chloride (Scheme 1.5) in isopropanol gave **1.25** selectively after 7 days through initial formation of the kinetically controlled product **1.24**. Compound **1.25** was unstable and could not be isolated in a pure state but kinetically controlled transacetalisation of **1.25** with acetyl chloride in methanol (rt, 4.5 h, 50% conversion) proceeded in a stereoselective manner to give a 60% isolated yield (based on consumed **1.25**) of **1.22** and a 14% yield of **1.26** (**1.26**:**1.22** = 4:1). The 10- α -isopropoxy compound was recovered in 42% yield in the form of a 6- α -methoxy compound **1.27**.



Scheme 1.5

Nakata and his associates discovered that reduction of the 7-*O*-benzoyl analogue of *N*-acyl imidate **1.20** with NaBH_4 in a mixture of isopropanol and CH_2Cl_2 gave **1.23** (28%) and **1.22** (30%) (Scheme 1.6).^{27, 28} The 10-*epi* derivative **1.22** was converted into **1.23** by reaction of **1.22** with 2-propanethiol and camphorsulfonic acid (CSA) in CH_2Cl_2 to give thioacetal **1.28** which was then treated with HgCl_2 in MeOH in the presence of NEt_3 to give **1.23** in 47% yield (from **1.22**) along with epimer **1.22** (36%). The completion of the synthesis was performed as previously described by Matsumoto.

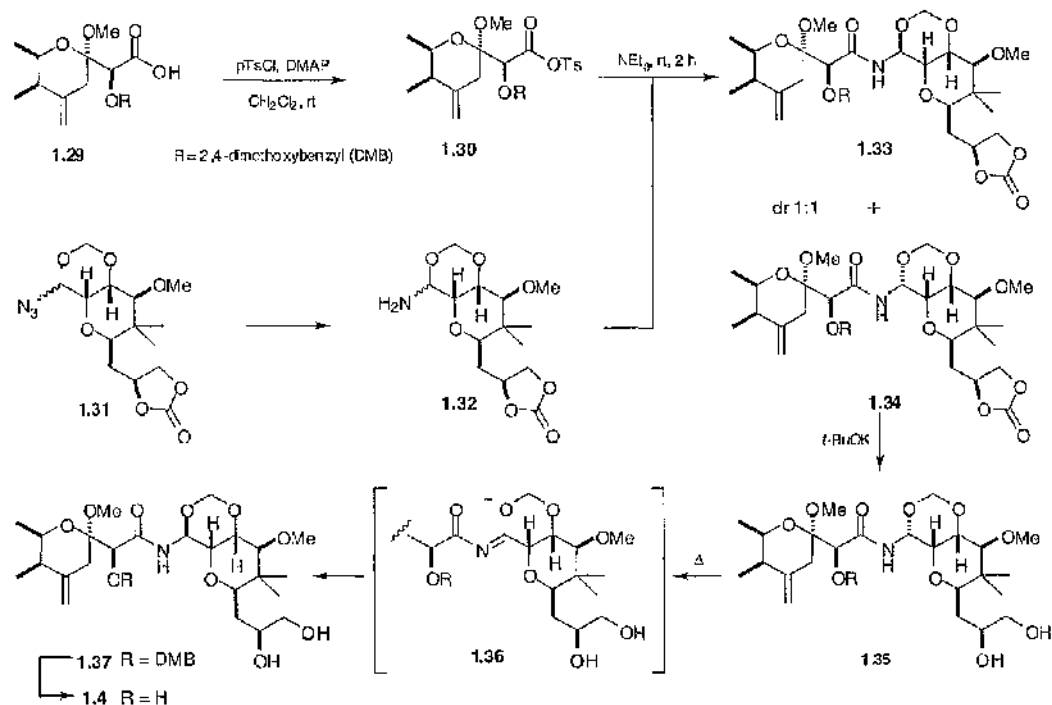


Scheme 1.6

1.2.2. The C8–N9 Connection via Amino Acylation.

In the Matsumoto–Nakata approaches to pederin, the *N*-acyl amino bridge was constructed by first condensing an activated carboxylic acid (e.g. acid chloride **1.13**) with an imidate ester to give an *N*-acyl imidate which was reduced with sodium borohydride to generate the *N*-acyl amino— a reaction which gave poor stereoselectivity. In the mycalamides, onnamides and theopederins, the incorporation of the oxygen atom of the amino into a

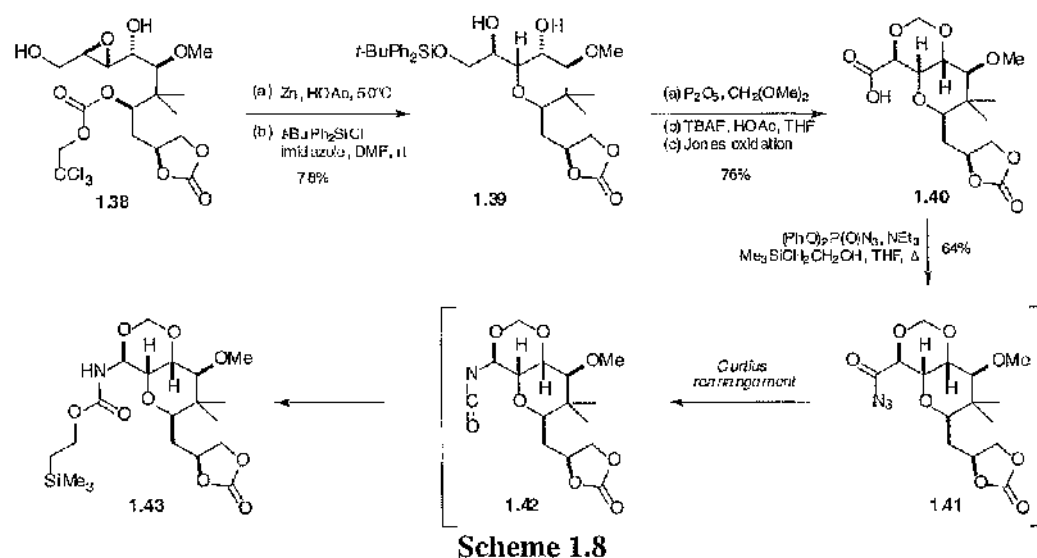
dioxane ring makes the Matsumoto–Nakata protocol less attractive owing to the difficulty associated with the synthesis of the appropriate imidate ester. Therefore, the first syntheses of mycalamide A, mycalamide B³⁴ and onnamide A³⁹ by Kishi and Hong adapted the Matsumoto–Nakata protocol by condensing an aminoral **1.32** with the activated carboxylic acid derivative **1.30** as illustrated in Scheme 1.7. The C10 aminoral unit of **1.32** is configurationally unstable under acidic, basic, and neutral conditions, and consequently a 1:1 mixture of adducts **1.33** and **1.34** was obtained. However, treatment of **1.34** with potassium *tert*-butoxide at room temperature first accomplished the transesterification of the carbonate group of **1.34** to the corresponding diol **1.35** which then epimerised on heating to yield **1.37**. Owing to competing decomposition, the reaction was stopped at approximately 60% completion to yield the epimerised natural diastereoisomer **1.37** in 42% yield along with the unnatural diastereoisomer **1.35** (33% yield). Nakata has also described a synthesis of mycalamide A in which the *N*-acyl aminoral bridge is constructed by the Kishi procedure.³⁶



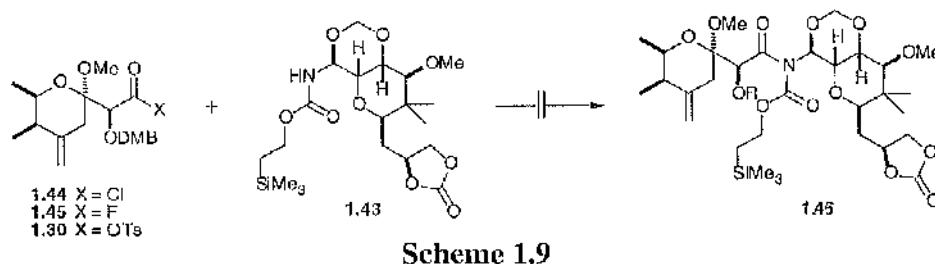
Scheme 1.7

In 1993 Roush and co-workers described a route to the mycalamides which incorporates two significant advances.⁴⁷ Firstly, the stereochemistry of the aminoral was assured by a Curtius rearrangement and secondly, the configuration of the aminoral centre was stabilised as a temporary carbamate appendage. The steps leading up to the Curtius rearrangement are noteworthy. Reductive cleavage of the 2,2,2-trichloroethyl carbonate **1.38** (Scheme 1.8) with Zn released an alkoxide which performed a nucleophilic attack on the neighbouring oxirane to give a cyclic diol which was selectively protected as its mono-*tert*-

butyldiphenylsilyl ether **1.39**.⁵⁰ After closure of the 1,3-dioxane ring, the *tert*-butyldiphenylsilyl ether was cleaved and the resultant alcohol oxidised to the corresponding carboxylic acid **1.40**. The key Curtius rearrangement was performed by treatment of acid **1.40** with diphenylphosphoryl azide at 65 °C. The intermediate acyl azide **1.41** underwent the desired Curtius rearrangement with clean retention of configuration to the isocyanate **1.42** which was trapped with 2-trimethylsilylethanol to give the carbamate **1.43** as a single diastereoisomer. Hoffmann published an approach to the trioxadecalin ring system of the mycalamides in 1993 which was similar to that of Roush, in that it included a Curtius rearrangement to form the C10-aminal diastereoselectively.⁴⁸

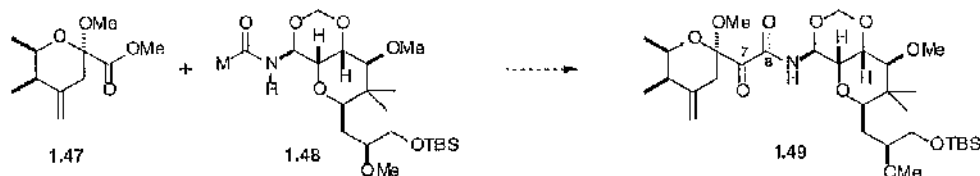


Roush and co-workers later published a very brief route to the pederic acid derivatives **1.44**, **1.45** and **1.30** and they achieved some success in the construction of *N*-acyl aminal bridges with model systems but the high steric hindrance of the carboxyl group in the left fragments once again thwarted condensation with the carbamate **1.43** (Scheme 1.9) under a wide variety of conditions and none of the desired adduct **1.46** was observed.^{51, 53, 58}



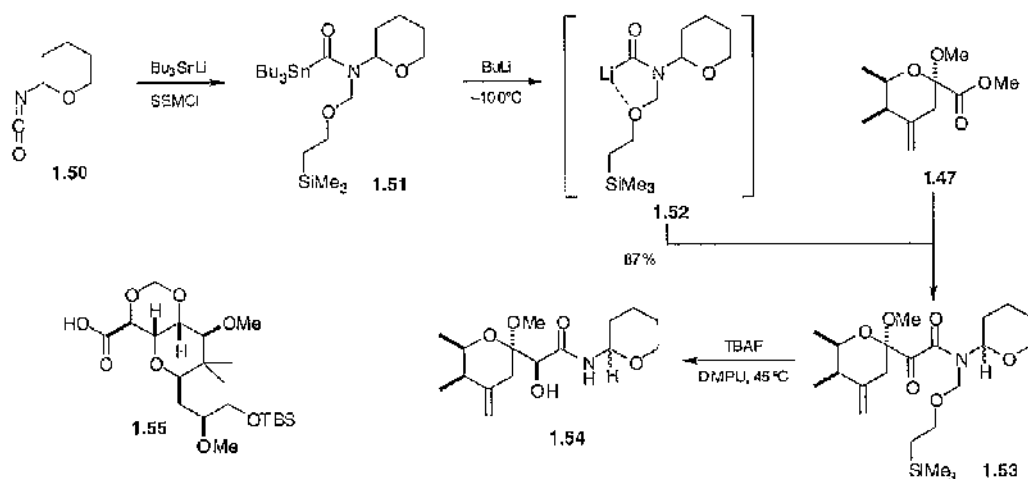
1.2.3. The C7–C8 Connection.

In 1996 Hoffmann proposed an original strategy to the construction of the *N*-acyl aminal bridge of mycalamide B based on union of the ester **1.47** with the acyl anion **1.48** to forge the C7-C8 bond (Scheme 1.10).⁵⁹ Once again, the stereochemistry of the aminal is to be controlled by a Curtius rearrangement.



Scheme 1.10

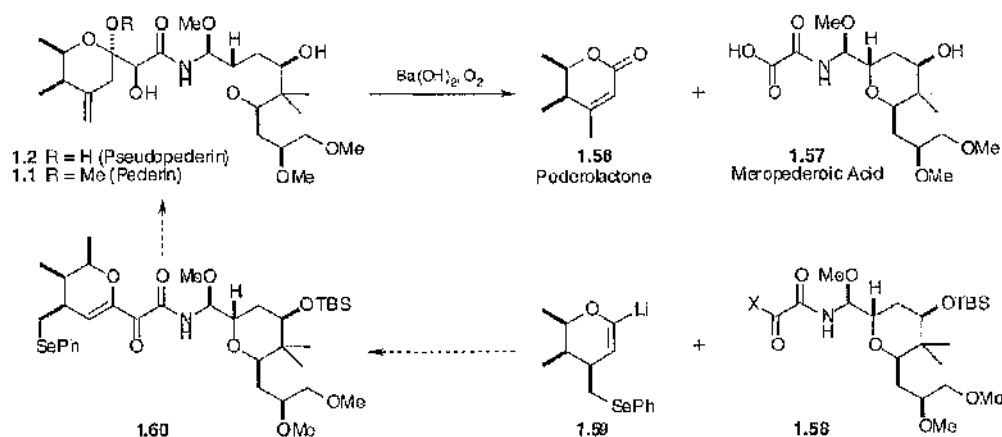
Model studies for the novel coupling step were carried out with the commercially available isocyanate **1.50** as a surrogate for the right fragment. The acylstannane **1.51** (Scheme 1.11) protected as its 2-(trimethylsilyl)ethoxymethoxy (SEM) derivative was easily prepared by addition of Bu_3SnLi to the isocyanate **1.50** followed by *N*-alkylation with 2-(trimethylsilyl)ethoxymethyl chloride. The use of SEM protection for the N-atom was a judicious choice whose purpose was stabilisation of the highly labile acyllithium **1.52** which was generated and trapped *in situ* by transmetalation with BuLi at -100°C . The desired model adduct **1.53** was obtained in 87% yield. A fortuitous and unprecedented reduction of the α -oxo ester accompanied the deprotection of the SEM group in adduct **1.53** with TBAF in *N,N'*-dimethylpropyleneurea (DMPU) to give the desired α -hydroxyamide **1.54** as mixture of diastereoisomers (dr 3:1). The origin of the hydride for the reduction of the keto function is unknown. Progress towards implementation of the strategy has been reported: a synthesis of **1.55** from D-arabinose has been accomplished⁵⁵ but union of the fragments remains elusive.



Scheme 1.11

1.2.4. The C6–C7 Connection: The Metallated Dihydropyran Approach.

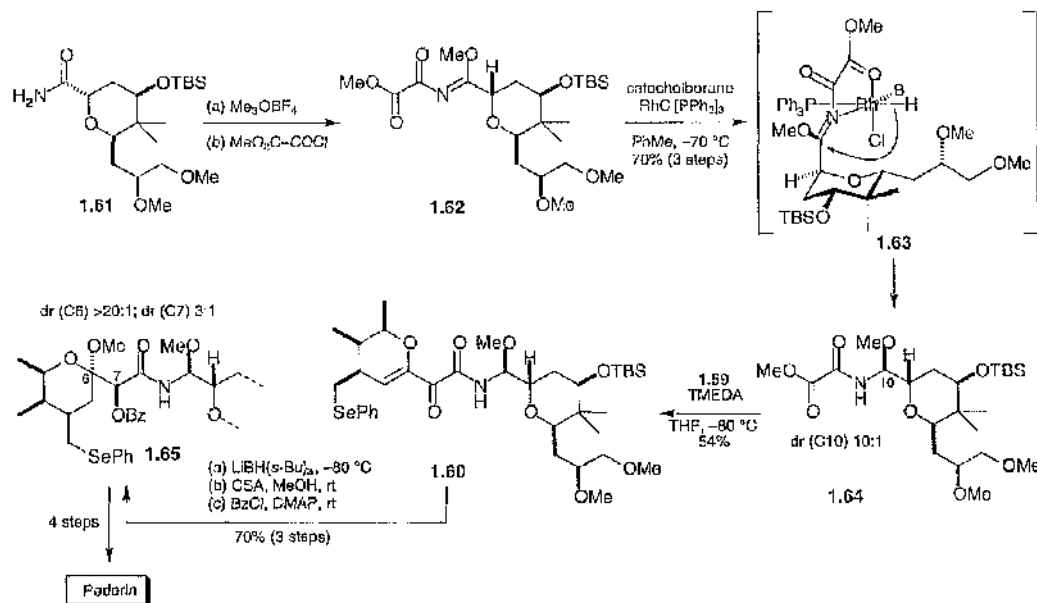
In our early approaches to the synthesis of pederin, we chose the well-trodden Matsumoto-Nakata protocol for the construction of the *N*-acyl aminal bridge.^{29, 40-42, 44, 45} We were similarly chastened by difficulty in reconciling slow reactions with unstable reagents which has been a persistent feature of nearly all of the accounts reported to date. Moreover, the problem was compounded by the poor stereoselectivity of the subsequent reaction of the *N*-acyl imidate adducts. In the mid-1980's we turned to a new strategy which attempted to alleviate the problems associated with the high steric hindrance surrounding the acetal centre at C6. Our new strategy was inspired by some of the elegant degradation studies conducted by Quilico during their structure elucidation of pederin.¹⁰ Pseudopederin (**1.2**, Scheme 1.12), the hydrolysis product of pederin, undergoes an easy retroaldol reaction on heating in base in presence of air to give pederolactone (**1.56**) and meropederic acid (**1.57**) wherein the *N*-acyl aminal group is still intact. These transformations suggested an alternative disconnection between C6 and C7 that circumvented the cascade of problems which beset the closing stages of the previous syntheses. The new strategy required a metallated dihydropyran **1.59** functioning as an acyl anion equivalent in reaction with a suitably activated meropederic acid derivative **1.58**.^{31, 32}



Scheme 1.12

Amide **1.61** was converted to the *N*-acylimidate **1.62** in 2 steps using standard transformations. The imidate ester intermediate **1.62** was prone to hydrolysis but good yields were obtained by working fast and with minimal purification. Reduction of the *N*-acylimidate **1.62** was achieved by using an unprecedented reaction—reduction with catecholborane in the presence of a catalytic amount of $[\text{Ph}_3\text{P}]_3\text{RhCl}$. Under these conditions a 70% yield of a mixture of diastereoisomeric *N*-acyl amins was obtained in which the desired isomer **1.64** predominated (10:1). Thus, for the first time, a metal hydride reduction of an *N*-acyl imidate in the pederin series afforded appreciable selectivity in favour of the desired diastereoisomer at C10. The stereochemistry of the

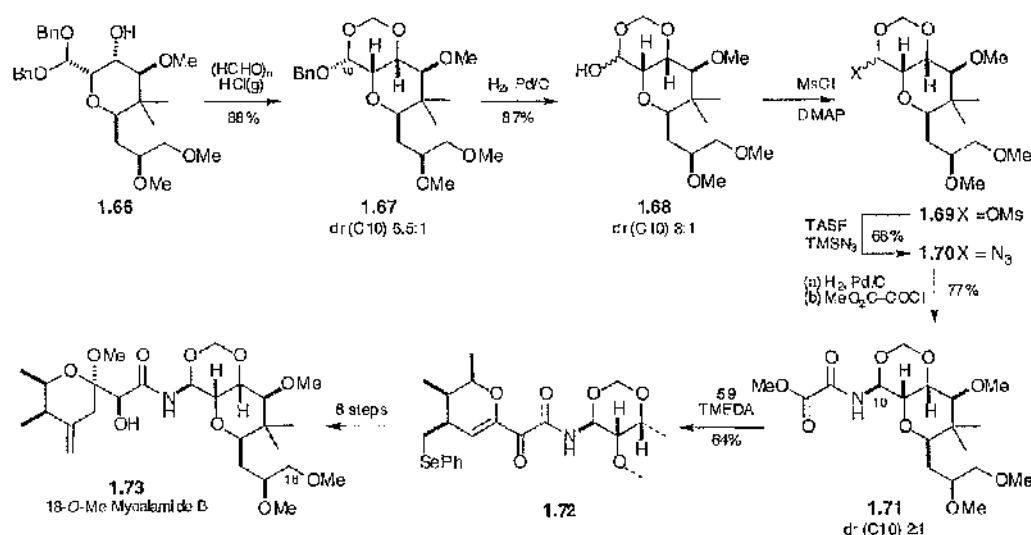
reduction was interpreted in terms of an intermediate **1.63** in which an octahedral Rh complex delivers a hydride intramolecularly as indicated in Scheme 1.13.



Scheme 1.13

The key reaction of the sequence entailed addition of the metallated dihydropyran **1.59** to the methyl ester **1.64** in the presence of TMEDA at low temperature to give a 54% yield of the adduct **1.60**. With the bulk of the pederin skeleton now constructed, completion of the synthesis merely required the introduction of the two adjacent stereogenic centres at C6 and C7 and a few functional group transformations. The stereogenic centre at C7 was introduced by metal hydride reduction of the enone function in **1.60**. Use of the bulky reducing agent $\text{LiBH}(\text{s-Bu})_3$ afforded the desired diastereoisomer in modest diastereoselectivity (3:1). Addition of methanol to the dihydropyran occurred with excellent diastereoselectivity ($\geq 20:1$). Completion of the synthesis required 4 further steps which were well preceded.

The success of the metallated dihydropyran approach in the synthesis of pederin suggested an easy adaptation of the strategy to syntheses in the mycalamide-theopederin series. An initial foray published in 1996 was superseded by tactical improvements depicted in Scheme 1.14 for the synthesis of 18-*O*-methyl mycalamide B⁶⁰, which had been identified as the most potent of the mycalamide derivatives in assays against a series of human tumours^{61, 62} (see below). The construction of the 1,3-dioxane ring was accomplished by treatment of **1.66** with paraformaldehyde in the presence of HCl to give a mixture of diastereoisomeric 1,3-dioxane acetals **1.67** (dr = 6.5:1) in 88% yield. Separation of acetals **1.67** by column chromatography was possible but useless since hydrogenolysis of the benzyl group gave the same mixture of hemiacetals **1.68** (dr 3:1).

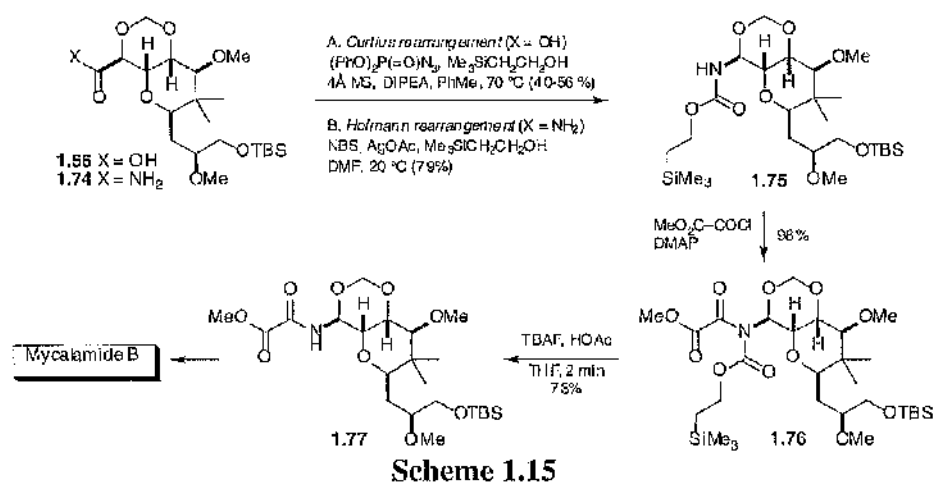


Scheme 1.14

Replacement of the hydroxyl group in **1.68** by an azido group *via* substitution of the mesylate **1.69** by Bu₄NN₃³⁴ had been reported by Hong and Kishi³⁴ but in our hands the yields ranged from 20% (typically) to 72% (rarely). We therefore developed a new method which, to our knowledge, is novel: the crude mesylate **1.69** derived from the mixture of hemiacetals **1.68** was treated with trimethylsilyl azide in the presence of tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF) to give the azides **1.70** as a mixture of diastereoisomers in the ratio 1:1 to 2:1 depending on the reaction conditions. The isomers could be separated for purposes of characterisation but in practice it was best to carry the mixture of azides forward to the next stage of the synthesis. Catalytic reduction of the azides **1.71** gave a sensitive mixture of amins which were acylated with methyl oxalyl chloride in the presence of DMAP to afford the diastereoisomeric methyl oxalamides (**1:2**) in 77% yield. The diastereoisomers were separated by column chromatography and the minor crystalline diastereoisomer **1.71** having the correct stereochemistry at C10 was added to a solution of the dihydro-2*H*-pyranyllithium reagent **1.59** in the presence of excess TMEDA to give the acylated dihydro-2*H*-pyran derivative **1.72** in 64% yield. The remainder of the synthesis was conducted as described above for the synthesis of pederin.³²

The successful implementation of the metallated dihydropyran approach to 18-*O*-methyl mycalamide B (Scheme 1.14) was gratifying but the unfavourable stereochemistry at the C10 aminal centre was a blemish which eluded correction. Therefore, we examined the Roush-Hoffmann Curtius protocol as part of a synthesis of mycalamide B.³⁸ Treatment of the carboxylic acid **1.55** (Scheme 1.15) with diphenylphosphoryl azide afforded an acyl azide intermediate which rearranged to an isocyanate which was trapped by 2-

(trimethylsilyl)ethanol to give the carbamate **1.75**. However, the elevated temperatures (70 °C) required for the rearrangement resulted in some decomposition with an overall reduction in yield to 56% at best with typical yields being more like 40%. A much better alternative was a classical Hofmann rearrangement using Ag(I)-assisted rearrangement of the *N*-bromoamide derived from amide **1.74**.⁶³ The reaction occurred at room temperature with clean retention of configuration to give the carbamate **1.75** in 79% overall yield. The remaining 2-carbon fragment was installed by reaction of carbamate **1.75** with methyl oxalyl chloride in the presence of DMAP to yield the imide derivative **1.76**. To complete the sequence, the carbamate function was expunged using TBAF buffered with acetic acid to give the *N*-acyl aminal intermediate **1.77** of mycalamide B. A similar strategy was used in the first synthesis of a member of the theopederin family, theopederin D (**1.7D**).³³



1.3. Biological Activity

1.3.1. The Natural Products.

Pederin is a very weak antibacterial agent but it is highly toxic to eukaryotic cells. Ingestion can cause severe internal damage and intravenous injection causes death at levels which suggest that it is more potent than cobra venom. The toxicity of pederin appears to be related to its inhibition of protein biosynthesis and cell division. Using human tonsil ribosomes, Vazquez^{64, 65} showed that pederin binds irreversibly to the ribosome preventing translation of mRNA. Inhibition occurred at the translocation step during the elongation cycle. The irreversible binding of pederin to ribosomes and its vesicant activity suggest it may function as an alkylating agent with the homoallylic acetal or *N*-acyl aminal as sites of potential reactivity. The biochemical and pharmacological activities are probably not related, however, since the hydrogenated derivative dihydropederin is not a vesicant though it remains a potent inhibitor of protein biosynthesis. Unfortunately there have been

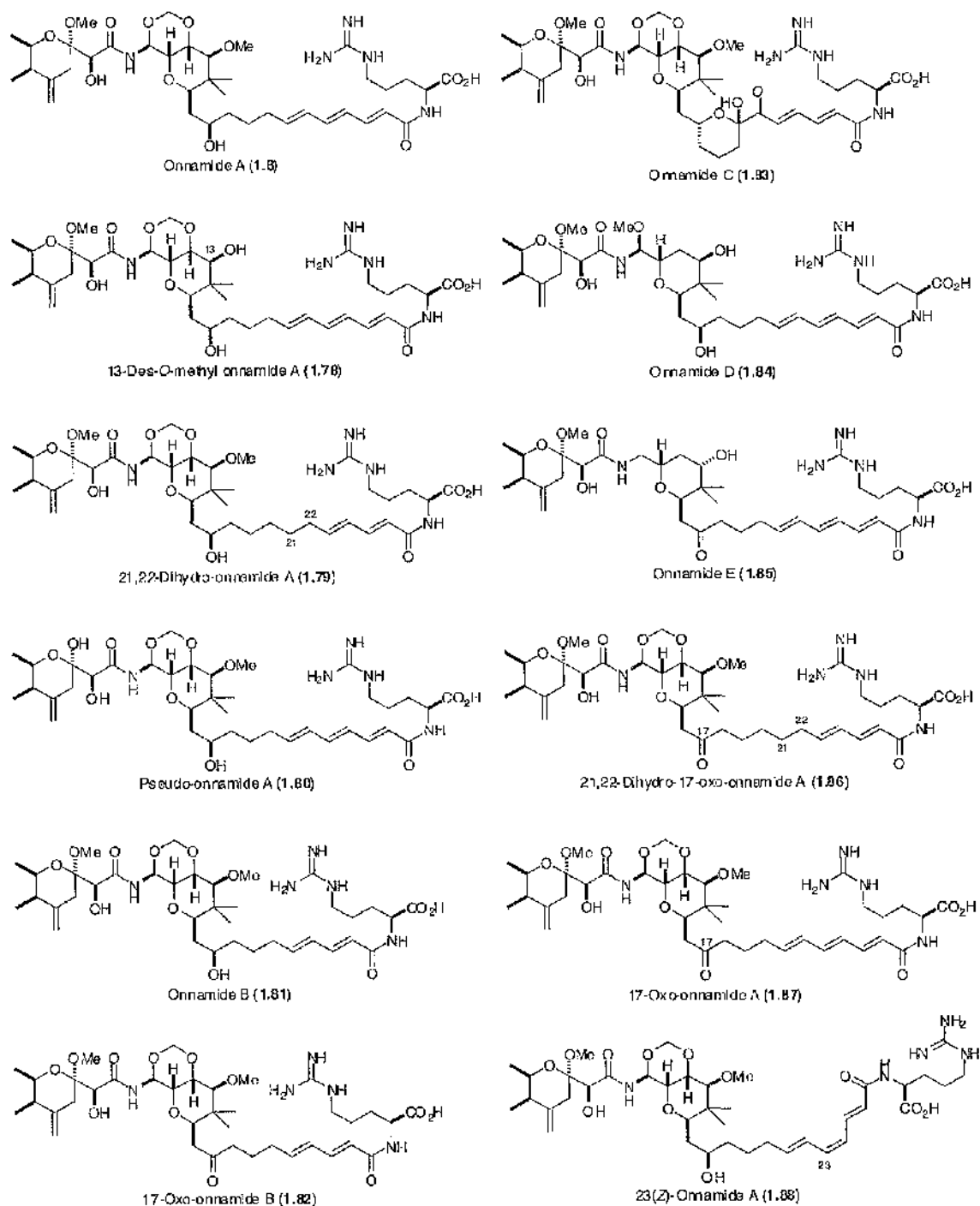
very few attempts to evaluate the clinical potential of pederin. Pavan⁶⁶ demonstrated that elderly patients with chronic necrotic and purulent sores completely recovered in some cases after treatment with minute amounts of pederin. A Russian study has also revealed a therapeutic effect on eczema and neurodermatitis with no complications.⁶⁷ Potential use as an anti-cancer agent has been suggested based on pederin's ability to block mitosis in normal and tumour cells at doses of 1 ng/ml and reports that it inhibited sarcoma-180 tumours in mice.⁶⁸

Like, pederin, the mycalamides and their derivatives induce severe dermatitis. Mycalamides A and B reveal potent *in vitro* cytotoxicity and *in vivo* antitumour efficacy against several leukemia and solid tumour model systems as well as antiviral activity. They inhibit *in vitro* replication of murine lymphoma P388 cells (IC_{50} 3.0 ± 1.3 and 0.7 ± 0.3 ng/ml respectively and human promyelocytic (HL-60), colon (HT-29) and lung (A549) cells ($IC_{50} < 5$ nM).⁶⁹ Mycalamide A was also active against B16 melanoma, Lewis lung carcinoma, M5076 ovarian carcinoma, colon 26 carcinoma, and the human MX-1 (mammary), CX-1 (colon), LX-1 (lung) and Burkitt's lymphoma tumour xenografts.⁶⁹ Mode of action studies confirm that the mycalamides, like pederin, are protein synthesis inhibitors. Mycalamide A also disrupts DNA metabolism but does not intercalate into DNA itself. A correlation between their relative ability to inhibit protein synthesis, cytotoxicity and their *in vivo* efficacy suggests that their anti-tumour activity is a consequence of protein synthesis inhibition.⁶⁹

Antiviral assays on mycalamide A by the Munro group^{17, 18} indicated that the minimum dose that inhibited the cytopathic effect of the test viruses (*Herpes simplex* Type-1 and *Polio* Type-1 viruses) over a whole (17 mm) well was 5 ng/disk. No *in vivo* antiviral results on pure mycalamide A were available from the initial screen but *in vitro* assays showed that it was responsible for the *in vitro* activity of the crude sponge extract and thus probably the *in vivo* activity as well. A crude extract (ca 2% mycalamide A) was tested in mice infected with A59 coronavirus. Four mice dosed with virus and the extract at 0.1 mg/kg survived 14 days whilst eight mice dosed with the virus only all died within 8 days. For further data relevant to the antiviral activity of mycalamide A see section 1.3.4.

Onnamide A is approximately equivalent in potency to mycalamides A and B against murine P388 leukemia cells (IC_{50} 2.4 ± 0.3 nM) *in vitro* but it was inactive against P388 cells *in vivo* (15% increase in life span at 40 μ g/kg). Onnamide A is about 70-fold less active against HL-60, HT-29 and A549 in line with its reduced potency as an inhibitor of protein synthesis.⁶⁹ Biological data for the remaining members of the onnamide sub-family is limited to *in vitro* studies against P388 and the relevant data is collected in Table 1.1. Onnamide A and 23(Z)-onnamide A (**1.88**, Scheme 1.16) are the most potent members of the family whilst onnamide E (**1.85**), lacking the *N*-acyl aminal functionality, is inactive. All members of the onnamide sub-family were vesicants.²⁰ There is also very little data

published regarding the antiviral activity of the onnamides. In their original report on the isolation and structure determination of onnamide A, Iliga et al¹⁹ claimed potent antiviral activity against *Herpes simplex* Type-1, vesicular stomatitis virus and coronavirus A-59.



Scheme 1.16

Theopederins A-E (1.7A–E) were markedly cytotoxic against P388 leukemia cells (see Table 1.1).²² Theopederins A and B also showed promising antitumour activity

against P388 (i.p.): T/C = 205% (0.1 mg/kg/day, treated on days 1, 2, and 4–6, i.p.) and T/C = 173% (0.4 mg/kg/day, treated on days 1,2 and 4–6, i.p.), respectively.

Table 1.1. IC₅₀ values (ng/ml) *in vitro* for members of the pederin family against murine P388 leukemia cells.

Compound ^a	Munro ^b	Fusetani ^c	Fusetani ^d	Kobayashi ^e
Pederin (1.1)	0.07	—	—	—
Mycalamide A (1.4)	0.5	—	—	—
Mycalamide B (1.5)	0.1	—	—	—
Theopederin A (1.7A)	—	0.05	—	—
Theopederin B (1.7B)	—	0.1	—	—
Theopederin C (1.7C)	—	0.7	—	—
Theopederin D (1.7D)	—	1.0	—	—
Theopederin E (1.7E)	—	9.0	—	—
Onnamide A (1.6)	0.4	—	10	2.0
13-des- <i>O</i> -Methyl-onnamide A (1.78)	—	—	150	—
21,22-Dihydro-onnamide A (1.79)	—	—	40	4.6
Pseudo-onnamide A (1.80)	—	—	130	—
Onnamide B (1.81)	—	—	130	—
17-Oxo-onnamide B (1.82)	—	—	100	—
Onnamide C (1.83)	—	—	70	—
Onnamide D (1.84)	—	—	20	—
Onnamide E (1.85)	—	—	inactive	—
21,22-Dihydro-17-oxo-onnamide A (1.86)	—	—	—	16.0
17-Oxo-onnamide A (1.87)	—	—	—	9.2
4(Z)-Onnamide A (1.88)	—	—	—	1.5

^a For structures see Schemes 1.1 and 1.16. ^b Reference 18 and 62. ^c Reference 22. ^d Reference 20. ^e Reference 21. Murine L1210 lymphoma cells were used.

1.3.2. Simple Derivatives of the Natural Mycalamides.

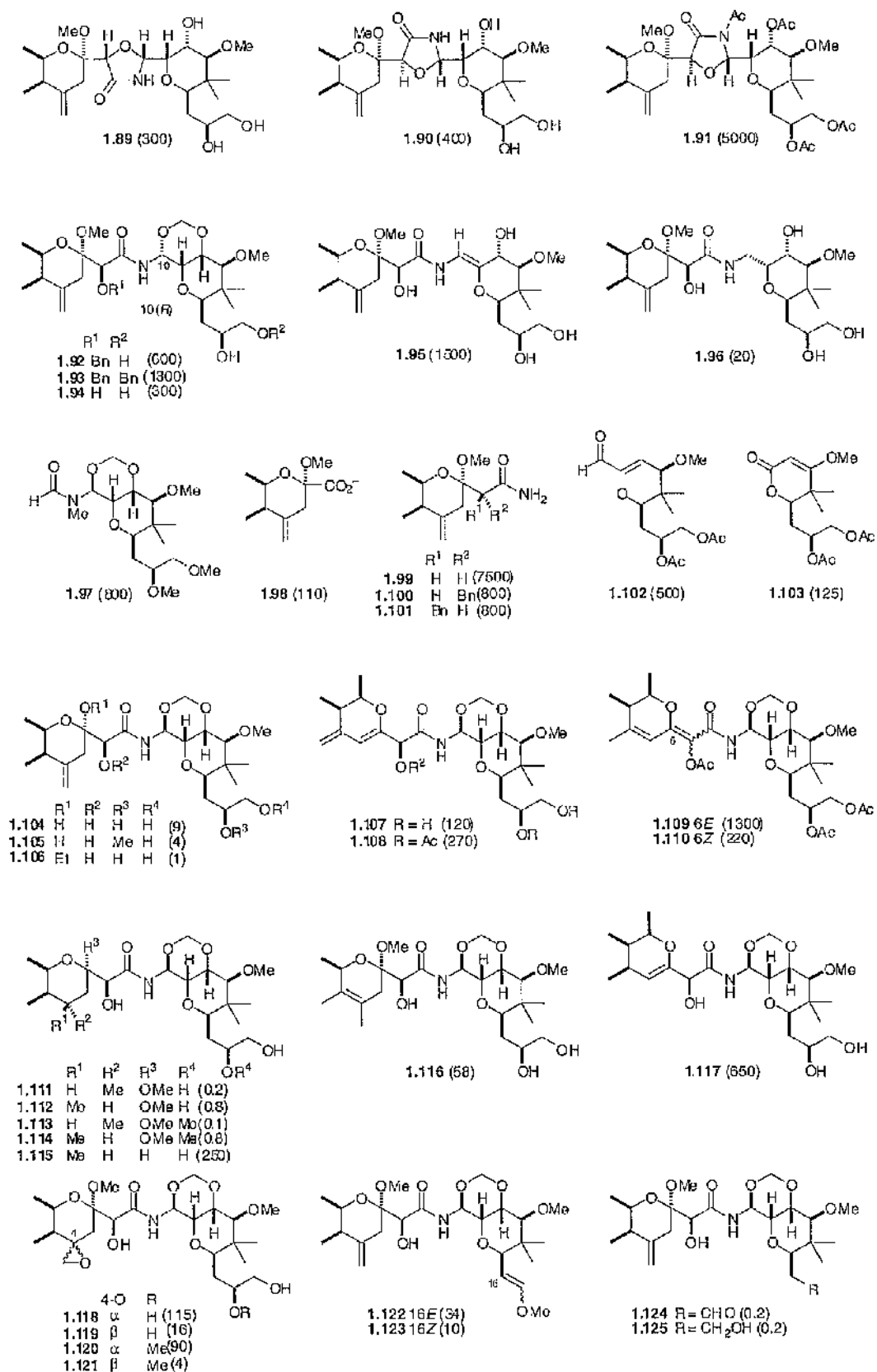
In 1992, Munro et al.⁶² prepared 34 simple acyl, alkyl and silyl derivatives of the C7, C17 and C18 hydroxyl groups and the *N*-amido group of mycalamides A and B and their relative potency assayed *in vitro* against P388 cells. The most noteworthy conclusions from this study are (a) methylation of the amide nitrogen together with the C7 hydroxyl group causes at least a 10³-fold reduction of activity; (b) derivatisation of the C7 hydroxyl group causes a 10–100 fold reduction in activity; and (c) methylation of both the C17 and C18 hydroxyl groups (as found in pederin) renders the mycalamides as active as pederin. From these observations Munro concluded that the intact *N*-acyl aminal bridge is vitally important for the biological activity of the mycalamides.

In 1997 we studied the biological activities of 18-*O*-methyl mycalamide B (1.73), 10-*epi*-18-*O*-methyl mycalamide B and pederin, all prepared by total synthesis.⁶¹ The activities of 18-*O*-methyl mycalamide B and pederin were virtually indistinguishable when evaluated in DNA or protein synthesis assays, and in cytotoxicity assays using human

carcinoma cell lines (IC_{50} s 0.2-0.6 nM). In the assays, 10-*epi*-18-*O*-methyl mycalamide B was 10^3 times less toxic than its diastereoisomer, demonstrating that the cytotoxicity of 18-*O*-methyl mycalamide B is inseparable from its ability to inhibit protein synthesis. Short-term exposure of squamous carcinoma cells to 18-*O*-methyl mycalamide B or pederin caused an irreversible inhibition of cellular proliferation and induced cellular necrosis. In contrast, the antiproliferative effects of the compounds on human fibroblasts were reversible and there was no evidence of necrosis.

1.3.3. Degradation Products of the Natural Mycalamides.

An extensive programme on the chemistry of the mycalamides by the New Zealand group of Munro and Blunt involved treatment of mycalamide A and some of its alkyl derivatives with alkoxide, hydroxide, oxide bases, sodium borohydride and azide.⁷⁰ The study was extended to acid-catalysed degradations, acetal exchange reactions, catalytic hydrogenation, epoxidation and oxidation reactions.⁷¹ The numerous derivatives and degradation products were then tested *in vitro* against P388 cells. The IC_{50} values in ng/ml are given together with the relevant structures in Scheme 1.17.



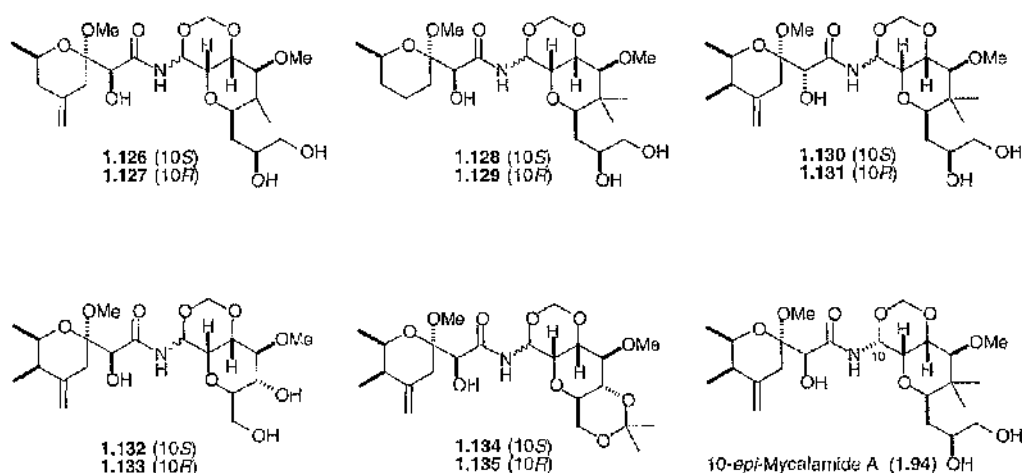
Scheme 1.17

Oxazolidinones **1.89-1.91** and the 7-*O*-benzyl derivatives **1.92** and **1.93** displayed poor activity as expected from the previous studies which had established the need for a free hydroxyl group at C7. The relative inactivity of the cleavage fragments **1.97-1.103** demonstrates further that both segments of the mycalamide structure are essential to the biological activity. Only the reduction product **1.96** (40-fold deactivation) has a significant biological activity, showing that the C10 configuration was crucial for activity to be displayed. The moderate activity of the reduction product **1.96** is surprising since the amination function is generally considered a crucial structural motif for biological activity. The importance of the C6 acetal is shown by the retention of activity with a C6 ethoxy derivative **1.106**, a 20-40-fold drop in activity for a C6 hydroxy substituent as in compounds **1.104** and **1.105** and further losses (> 100-fold) with elimination or hydrogenolysis at C6 (compounds **1.107-1.110**, **1.115**, **1.117**). Compounds involving derivatisation or transposition of the exocyclic double bond retained significant activity: thus, 4 β -dihydromycalamide A **1.111** was significantly more active than mycalamide A but 4 β -dihydromycalamide B **1.113** had the same activity as mycalamide B but Δ^3 -mycalamide A **1.116** was 100-fold less active than mycalamide A. The epoxide derivatives **1.118-1.121** were also much less active although there was an even more pronounced isomer effect.

Modifications at the C16 side chain were expected to be well tolerated so it was surprising that both Δ^{16} -normycalamide B isomers (**1.122** and **1.123**) were *ca* 100 fold less active than mycalamide B. However, the C17 aldehyde and alcohol derivatives (**1.124** and **1.125**) were significantly more active than both mycalamide A and theopederin E (IC₅₀ = 9 ng/mL against P388).

1.3.4. Advanced Synthetic Analogues of Mycalamide A

In 1997 the Nakata⁷² group synthesised a set of ten advanced analogues of mycalamide A (Scheme 1.18) in order to probe the minimum structural requirements of the left fragment for biological activity and to explore the possibility of replacing the right fragment with glucose derivatives. The cytotoxicity against HeLa cells and antiviral activity against *Herpes simplex* type1 (HSV-1) and Varicella-zoster virus (VZV) were tested *in vitro* along with 5-fluorouracil and acyclovir as standards. The data are summarised in Table 1.2. For comparison, parallel tests were run on mycalamide A itself and its 10-epimer (**1.95**).



Scheme 1.18

Table 1.2. Biological Activity of Mycalamide A Analogues^{a,b}

Compound	Cytotoxicity against HeLa cells	Antiviral activity against HSV-1		Antiviral activity against VZV	
	IC ₅₀	MIC ^c	IC ₅₀ ^d	MIC ^e	IC ₅₀ ^f
5-Fluorouracil	3.0	—	—	—	—
Acyclovir	—	1.6	1.6	6.25	>50.0
Mycalamide A (1.4)	<0.03	<0.4	<0.4	<0.4	<0.4
10- <i>epi</i> -Mycalamide A (1.94)	3.0	12.5	12.5	1.6	12.5
1.126	<0.03	<0.4	<0.4	<0.4	<0.4
1.127	3.0	50.0	50.0	1.6	>50.0
1.128	0.03	3.1	3.9	<0.4	1.6
1.129	>10.0	50.0	>50.0	3.1	>50.0
1.130	>10.0	50.0	12.5	<0.4	12.5
1.131	>10.0	50.0	>50.0	12.5	>50.0
1.131	1.0	25.0	25.0	3.1	>50.0
1.132	>10.0	>50.0	>50.0	25.0	>50.0
1.133	3.0	50.0	>50.0	12.0	>50.0
1.134	10.0	50.0	50.0	12.5	>50.0
1.135					

^a Data taken from Nakata *et al.*, ref 72. ^b IC₅₀ (μg/ml), MIC (μg/ml) ^c Against HSV-1 cells. ^d Against vero cells. ^e Against VZV. ^f Against HEL cells.

Mycalamide A, **1.126** and **1.128** showed very potent cytotoxicity against Hela cells but their corresponding 10-epimers (*i.e.* 10-*epi*-mycalamide A, **1.127** and **1.129**) were 100-fold less active suggesting that the C10 configuration is a crucial determinant for high cytotoxicity. As expected from the results described in the previous section, the high activity of compound **1.127** verifies that the presence of the C4-*exo*-methylene and C3-methyl groups are not an important factor for the potent cytotoxicity. The unnatural C7 hydroxyl isomers **1.130** and its C10-epimer **1.131**, decreased the activity, which suggests that the configuration of the C7-hydroxy group is also essential for potent cytotoxicity. It is

noteworthy that **1.132** and **1.134**, in which the right fragment is replaced by glucose derivatives, showed nearly the same activity as 5-fluorouracil.

A compound can be judged to have significant antiviral activity if its therapeutic ratio (TR = IC₅₀/MIC) is higher than that of acyclovir. The antiviral activity of mycalamide A, **1.126** and **1.128** against HSV-1 is very strong. However, their cytotoxicity (IC₅₀) against vero cells is also very strong: TRs of all synthetic compounds tested are less than 1 (TR of acyclovir = 32). Although mycalamide A, **1.126** and **1.127** showed strong activity against VZV, their potent cytotoxicity (IC₅₀) against HEL cells was also observed. 10-*epi*-Mycalamide A (**1.94**), **1.127**, **1.129**, **1.130**, and **1.132** showed potent antiviral activity against VZV and low cytotoxicity against HEL cells: TRs of 10-*epi*-mycalamide A (**1.94**), **1.127**, **1.129**, **1.130** and **1.132** are 8, >32, >16, >32, and >16, respectively (cf. TR of acyclovir >8). Thus 7- or 10-epimeric compounds showed significant antiviral activity against VZV.

1.3.5. Simple Synthetic Derivatives.

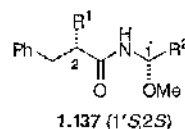
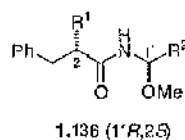
None of the biological data presented thus far identifies the *minimum* structural requirements for cytotoxicity or antiviral activity. In 1997, Abell *et al*⁷³ evaluated the cytotoxicity of simple analogues (Table 1.3) of the *N*-acyl aminal bridge against the P388 leukaemia cell line *in vitro*. In general, compounds **1.136a-i** with a (1'*R*,2*S*)-configuration (equivalent to C7 and C10 in the natural products) show significantly greater *in vitro* cytotoxicity than the corresponding (1'*S*,2*S*)-derivatives **1.137a-i**. Notable exceptions were the parent natural products (pederin, mycalamides A and B) for which the equivalent C10 position is *S*. A preference for a (1'*R*)-configuration over a (1'*S*)-configuration does not seem to be evident within the cyclic oxazolidinone series **1.138–1.143** (Scheme 1.19), where the (1'*S*)- and (1'*R*)-compounds show similar *in vitro* cytotoxicity.

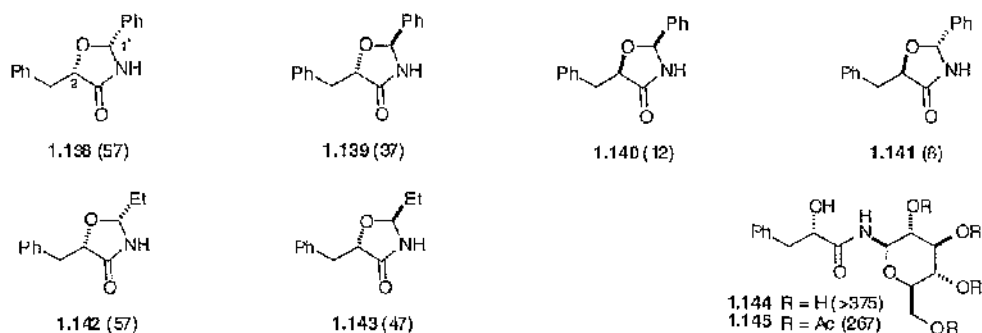
Table 1.3
IC₅₀ values of **1.136** and **1.137** against P388 cells

	R ¹	R ²	IC ₅₀ (μg/ml)	
			1.136 (1' <i>R</i> ,2 <i>S</i>)	1.137 (1' <i>S</i> ,2 <i>S</i>)
a	OH	Ph	52	>340
b	OH	Me	>125	>188 ^a
c	NHZ	Ph	14	>188 ^b
d	NH-Ak-Z	Ph	36	>125
e	OAc	Ph	101	>313
f	OH	Et	176	43
g	NHZ	Me	>375	>375
h	OCOC ₆ H ₄ Br	<i>i</i> -Pr	105 ^c	105
i	O-camphanyl	Ph	42 ^d	78 ^d

^a 1:1 mixture of epimers. ^b 3:1 mixture of epimers. ^c 17:3 mixture of epimers.

^d 9:1 mixture of epimers.



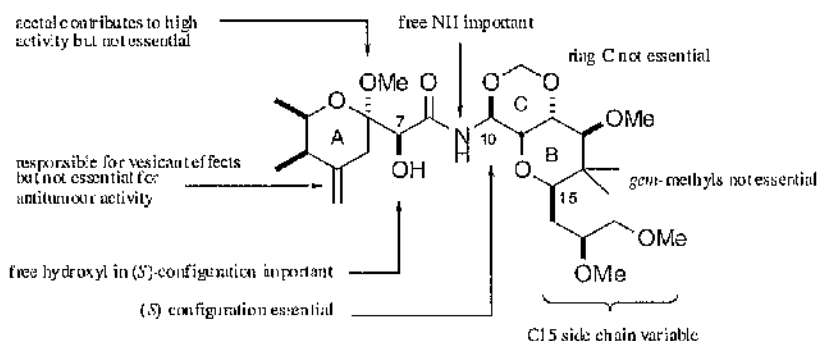


Scheme 1.19

A variety of R^1 groups appear to be accommodated for the induction of *in vitro* cytotoxicity. For example, the corresponding acetates of **1.136a** and **1.137a**, compounds **1.136e** and **1.137e**, show comparable activity. By comparison, acylation of the C7-hydroxyl group of mycalamide A and B (analogous to C2 in **1.136/1.137**) results in compounds with significantly decreased activity. The (1')-epimeric pairs **1.136c,d,g** and **1.137c,d,g** were designed to give the derivatives more peptide character. The most active compounds in this series, compounds **1.136c,d** show activities comparable to, or better than, **1.136a**. Again a preference for a (1'*R*)-configuration is noted (**1.136c/1.137c** and **1.136d/1.137d**). A change from $R^2 = \text{Ph}$ to Et appears to be tolerated, although in this case, contrary to the other compounds, a (1'*S*)-configuration seems to give the most potent *in vitro* bioactivity (**1.136f** > **1.137f**). It should be noted that **1.137f** and the parent natural products possess the same relative configuration at this centre (i.e. *S*). The introduction of a methyl group at the R^2 position resulted in compounds with significantly reduced activity (see compounds **1.136b,g**, **1.137b,g**). Finally, the glucosyl derivatives **1.143** and **1.144** show less activity than the corresponding acyclic analogues **1.136** and **1.137** where $R^2 = \text{Et}$ and Ph.

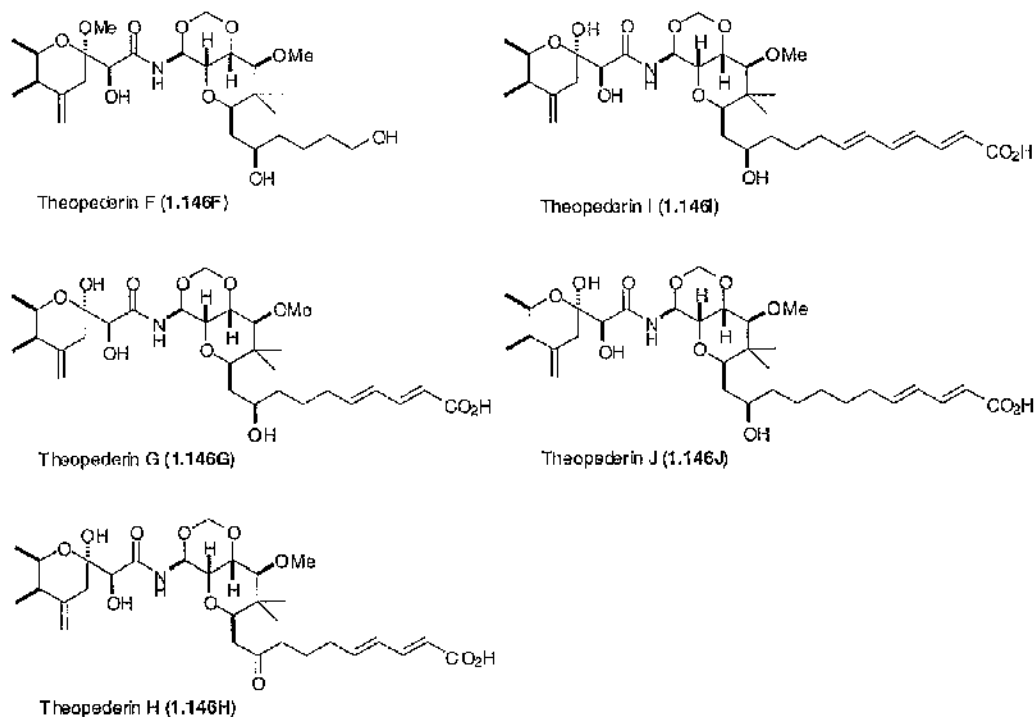
In conclusion, the foregoing structure activity studies on the pederin family of antitumour agents established that the *N*-acyl aminal bridge is the pharmacophore. The homoallylic acetal array encompassing C4–C6 which is responsible for the acid lability of the natural products as well as their vesicant effects, is not necessary for antitumour or antiviral activity. The C6 acetal function contributes to the high activity of the natural products though simpler analogue studies reveal that it is not essential. The presence of a free hydroxyl group at C7 with the (*S*)-configuration is important for high activity. The configuration of the aminal centre is also very important with the (*S*)-configuration at C10 being significantly more active as an antitumour agent than the (*R*)-epimer; however, compounds with the (*R*)-configuration at C10 remain potent antiviral agents. The complex trioxadecalin ring system characteristic of the mycalamides, onnamides and theopederins is not essential for high activity since pederin, with its simpler monocyclic right half, is one of the most active of the natural products followed closely by 18-*O*-methyl-mycalamide B,

a simple synthetic derivative of natural mycalamide B. Finally, the side chain at C15 tolerates considerable variation with comparatively little impact on activity. A summary of the SAR data is given in Scheme 1.20.



Scheme 1.20

Addendum. Theopederins F-J (**1.146F-J**, Scheme 1.21) have recently been isolated from *Theonella swinhoei*.⁷⁴ Theopederin F was antifungal against an *erg6* mutant of *Saccharomyces cerevisiae* deficient in (*S*)-adenosylmethionine: Δ^{24} -methyltransferase involved in the biosynthesis of ergosterol. Theopederin F was also cytotoxic against murine P388 cells with an IC_{50} of 0.15 ng/ml. No biological data was reported for theopederins G-J. The close structural kinship between theopederins G-J and the onnamides suggests that the theopederins may be biosynthetic precursors of the onnamides.



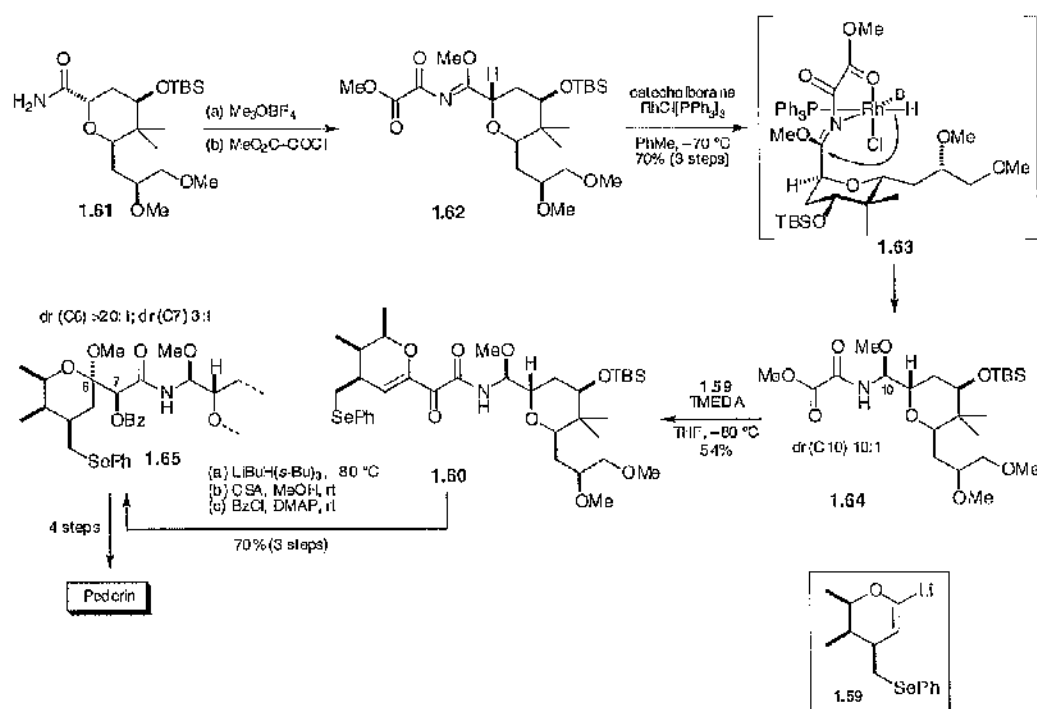
Scheme 1.21

Chapter 2 : Previous achievements in the Kocienski group and objectives

2.1 Previous achievements in the Kocienski group

2.1.1 Lithiated dihydropyran approach

During the early work on the synthesis of pederin **1.1**, Jarowicki and Marczak were faced with the task of constructing the *N*-aminal bridge. As shown in Chap 1, Sec 2.4, they completed the synthesis of pederin **1.1** using the metallated dihydropyran approach (Scheme 2.1) and they also optimised the installation of the stereogenic centres at C7 and C10.^{32, 75}



Scheme 2.1

Amide **1.61** was converted to the *N*-acylimide **1.62** in 2 steps using standard transformations. The imide ester intermediate **1.62** was prone to hydrolysis but good yields were obtained by working fast and with minimal purification. Reduction of the *N*-acylimide **1.62** was achieved by using an unprecedented reaction—reduction with catecholborane in the presence of a catalytic amount of $[\text{Ph}_3\text{P}]_3\text{RhCl}$. Under these conditions a 70% yield of a mixture of diastereoisomeric *N*-acyl aminals was obtained in which the desired isomer **1.64** predominated (10:1). Thus, for the first time, a metal hydride reduction of an *N*-acyl imide in the pederin series afforded appreciable selectivity in favour of the desired diastereoisomer at C10. The stereochemistry of the

reduction was interpreted in terms of an intermediate **1.63** in which an octahedral Rh complex delivers a hydride intramolecularly as indicated in Scheme 1.13.

The key reaction of the sequence entailed addition of the metallated dihydropyran **1.59** to the methyl ester **1.64** in the presence of TMEDA at low temperature to give a 54% yield of the adduct **1.60**. With the bulk of the pederin skeleton now constructed, completion of the synthesis merely required the introduction of the two adjacent stereogenic centres at C6 and C7 and a few functional group transformations. The stereogenic centre at C7 was introduced by metal hydride reduction of the enone function in **1.60**. Use of the bulky reducing agent $\text{LiBH}(\text{s-Bu})_3$ afforded the desired diastereoisomer in modest diastereoselectivity (3:1). Addition of methanol to the dihydropyran occurred with excellent diastereoselectivity ($\geq 20:1$). Completion of the synthesis required 4 further steps which were well precedented.

The success of the metallated dihydropyran approach in the synthesis of pederin suggested an easy adaptation of the strategy to syntheses in the mycalamide-theopederin series. This approach for the coupling of the two fragments has since successfully been applied to the synthesis of 18-*O*-methyl mycalamide B.^{60, 76}

2.2.2 Optimised access to lactone **2.1** and enone **2.4**

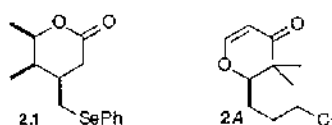


Figure 2.1

Unfortunately, the previous route to fragments **1.59** and **1.64** designed by Jarowicki and Marczak was expensive and impractical and therefore targeting the total synthesis of 18-*O*-methyl-mycalamide B, Smith and Raubo developed a very efficient synthesis of both lactone **2.1** and enone **2.4** (figure 2.1).⁷⁷ Their objectives were :

- To develop syntheses of the pederin family members using the well-precedented³² metallated dihydropyran approach to bridge the two fragments (see chapter 1, sec 2.4);
- To access these critical intermediates in high yields with good stereocontrol using large scale reactions;
- To use cheap starting materials, and avoid column chromatography instead of distillations or recrystallisations as main means of purification;
- To develop a flexible route that would allow access to several members of the pederin family and analogues.

Smith and Raubo had successfully applied their improved synthesis of **2.1** and **2.4** (chapters 3 and 4) towards the synthesis of 18-*O*-methyl mycalamide B⁷⁶, prior to the launch of the investigations described herein.

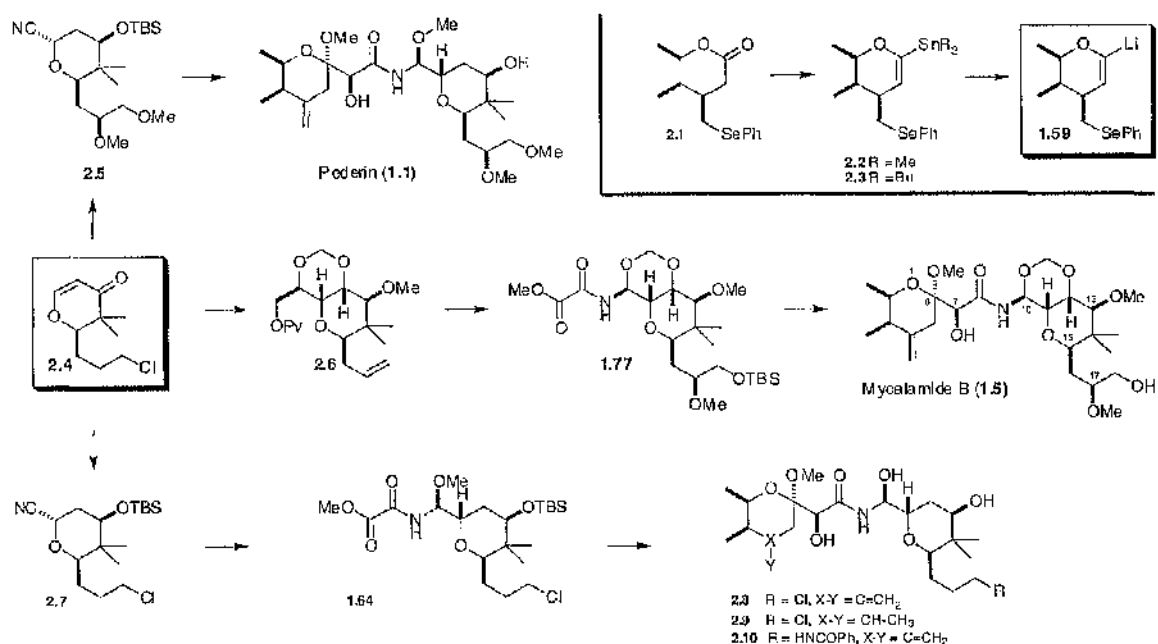
2.2 Objectives of the present work

1. To apply the aforementioned approach to **2.1** and **2.4** towards the design of an improved route towards pederin;
2. To complete and improve the total synthesis of mycalamide B.
3. To synthesise analogues of pederin in order to assess their biological activity.

However, a crucial requirement is to make use of the key aforementioned metallated dihydropyran approach in the synthesis of each member of the pederin family.

2.3 Synthetic strategy

As shown in scheme 2.2 the synthetic strategy for pederin **1.1**, mycalamide B **1.5**, 17-*epi*-mycalamide B, and analogues **2.8**, **2.9**, **2.10** uses the lithiated dihydropyran **1.59**^{32, 75}, which is accessed either from stannane **2.2** or **2.3**. Studies on the coupling reaction (Chapter 3) showed that the tributylstannane **2.3** is a more efficient intermediate than its trimethylstannane analogue **2.2**. Newly developed methodology, unpublished, has been used to access **2.3** by the reaction of a mixed cyano-stannyl cuprate with the enol triflate derived from lactone **2.1**. The key steps in the synthesis of pederin or its analogues are Sharpless asymmetric dihydroxylations and a rhodium-catalysed directed reduction of an acylimidate. The key steps in the synthesis of the right fragment of mycalamide B **1.5** are a P₂O₅-mediated formation of the trioxadecalin ring, a Meerwein-Ponndorf-Verley reduction to install the C13-stereogenic centre, installation of the C10-N bond in good yield and total stereocontrol at the C10 centre *via* a Curtius rearrangement and/or a Hofmann rearrangement, as well as Sharpless asymmetric dihydroxylations.



Scheme 2.2

Thereby, after a brief description of the synthesis of lactone **2.1**, formation and application of stannanes **2.2** and **2.3** to the coupling reaction will be discussed in chapter 3. Chapter 4 is devoted to a brief description of the synthesis of enone **2.4**, whereas chapters 5, 6, and 7 will detail the total (or formal) syntheses of pederin **1.1**, mycalamide B **1.5** (and its 17-epimer) and analogues **2.8-2.10** respectively. Finally, Chapter 8 is concerned with the biological activity of certain intermediates and synthetic members of the pederin family.

Chapter 3 Construction of the left fragment

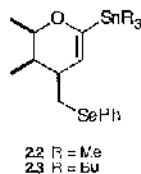
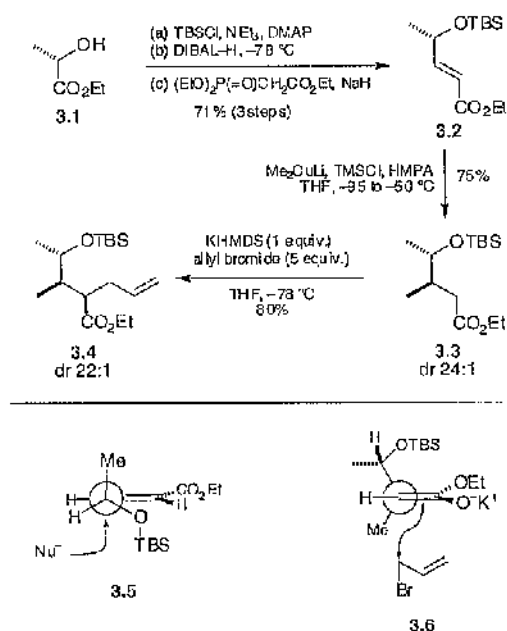


Figure 3.1

Vinyl stannane **2.2** is an intermediate, common to our synthesis of pederin **1.1** and mycalamide B **1.5**, and has been previously synthesised by Kocienski and co-workers during a synthesis of pederin **1.1**.³² The synthesis was too long and expensive; therefore, during the years 1996-1997, renewed efforts by Dr P. Raubo and Dr C. Smith concentrated on a more efficient synthesis of the lactone **2.1**. Lactone **2.1** was obtained in 13 steps from the cheap and readily available ethyl (*S*)-lactate (£1.60/mole) with nothing but distillations and recrystallisations as means of purification until reaching advanced intermediates. The key steps of this synthesis are a 1,4-conjugate addition of a methyl cuprate to homochiral enoate **3.2** and a diastereoselective allylation of the corresponding potassium enolate of β -methyl ester **3.3**.

3.1 Description of the synthesis of lactone **2.1**

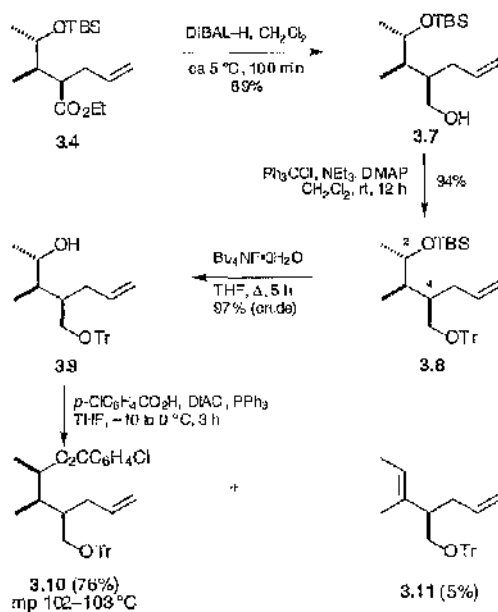
Ethyl (*S*)-lactate **3.1** was transformed in three simple steps to the α,β -unsaturated ester **3.2** in 71% overall yield on a 0.26 mol scale.⁷⁸ A diastereoselective conjugate addition of lithium dimethylcuprate to the ester **3.2** in the presence of HMPA and TMSCl at $-95\text{ }^{\circ}\text{C}$ ^{79, 80} afforded adduct **3.3** in 75% yield (dr 24:1). The final C-C bond forming reaction in the sequence was also highly diastereoselective. Alkylation of the potassium enolate of the ester **3.3** with allyl bromide gave the third contiguous stereogenic centre in **3.4** in 80% yield (dr 22:1) (scheme 3.2).



Scheme 3.2

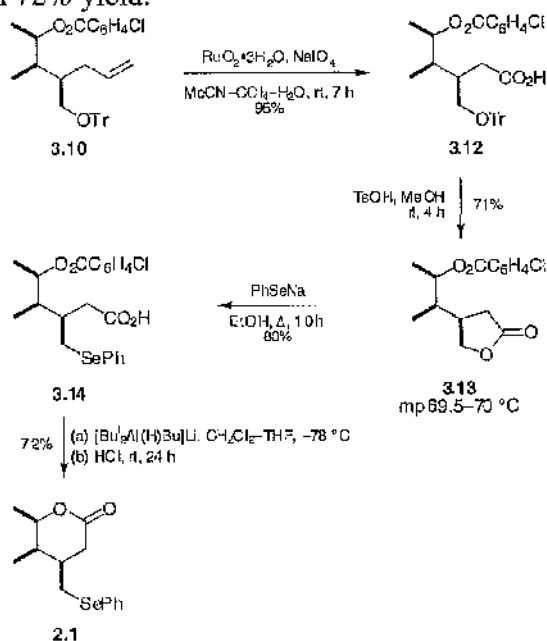
Ground state conformational models have been proposed to explain the stereoselectivity of the foregoing reactions. Yamamoto's model for the diastereoselective conjugate addition of various organocopper reagents to γ -alkoxy- α,β -unsaturated carbonyl derivatives places the best electron donating group perpendicular to the plane of the π -system and the OTBS group in the more sterically demanding "inside position".⁸⁰ The clear steric discrimination between the diastereotopic faces as indicated in structure **3.5** accounts for the anti attack of the nucleophile giving the anti-adduct **3.3**. Houk's "electrophilic rule" rationalises the diastereoselective alkylation of enolates with adjacent stereogenic centres.⁸¹ Thus the eclipsed conformation **3.6** placing the hydrogen of the stereogenic centre in the plane of the π -system again causes steric discrimination between the two diastereotopic faces of the enolate leading to alkylation as shown in structure **3.4**. Corroborating evidence for the Houk model has been presented.⁸²⁻⁸⁴

Routine transformations accomplished the conversion of **3.4** to the alcohol **3.9** (scheme 3.3) but the Mitsunobu reaction used to invert the configuration at C-2 (mycalamide numbering) in alcohol **3.9** was plagued by a competing elimination to give alkene **3.11**. A number of variations in carboxylic acid and azodicarboxylate ester eventually established that the combination of trityl as the protecting group, *p*-chlorobenzoic acid as the nucleophile, and diisopropyl azodicarboxylate as the activator returned the ester **3.10** in 76% yield together with only 5% of the elimination product **3.11** which was easily separated by column chromatography—the first in the sequence. Any minor diastereoisomers were easily separated by crystallisation of the *p*-chlorobenzoate **3.10**.



Scheme 3.3

Oxidative cleavage of the alkene **3.10** (scheme 3.4) followed by acid treatment achieved simultaneous trityl deprotection and lactonisation to give the second crystalline compound of the series, the lactone **3.13**. The phenylselenide group in **3.14** was introduced by nucleophilic substitution of the butyrolactone **3.13**.⁸⁵ Saponification of the *p*-chlorobenzoate ester in the usual way using hot 2 M NaOH was accompanied by an unexpected side reaction: epimerisation at C-2. Although the extent of epimerisation was small (ca 5%), suppressing it altogether was obtained by performing the cleavage with an "ate" complex derived from addition of BuLi to DIBAL-H.⁸⁶ The resultant hydroxy acid lactonised to give **2.1** in 72% yield.

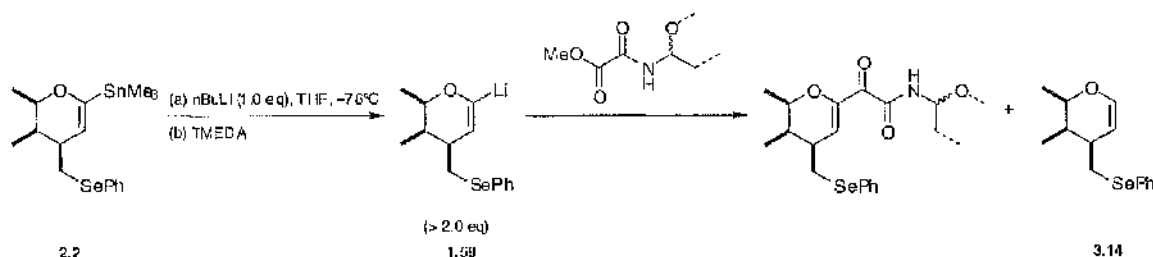


Scheme 3.4

3.2. Syntheses of stannanes 2.2 and 2.3 from lactone 2.1

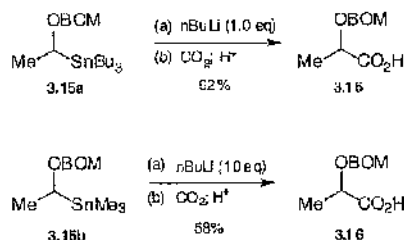
Conversion of lactone **2.1** to the trimethylstannane **2.2** had already been reported in our previous synthesis of pederin^{32, 75} by a 3-step sequence (yield 70%). The conversion involves a Pd(0)-catalysed Stille coupling between the enol triflate intermediate **3.21** and the expensive and toxic hexamethylditin (£19.70/g) as shown in scheme 3.8. This approach was used in the synthesis of pederin, mycalamide B, and 17-epi-mycalamide B (chapters 4-6).

Two aspects of the coupling reaction require further comment. First, the method used here is inherently wasteful, since one equivalent of lithiated dihydropyran **1.59** was squandered in abstracting the amide proton. Attempts to improve the stoichiometry by using a sacrificial lithium reagent (BuLi) in model systems were foiled by rapid competing addition of the butyllithium to the oxalamide. Secondly, the yield of the coupling was variable; whilst a 40% yield is typical, >70% was also obtained in related systems (scheme 3.5). Success in this reaction was experimentally related to the amount of transmetallated dihydropyran (estimated by TLC) which was variable as well. Literature studies on transmetallation between trimethylstannanes and tributylstannanes led us to compare their reactivities on our substrates.



Scheme 3.5

Indeed, J. M. Chong in 1998 showed that α -alkoxyorganotrimethylstannanes do not undergo transmetallations as well as their tributyl analogues.⁸⁷ Scheme 3.6 exemplifies the difference in reactivity.

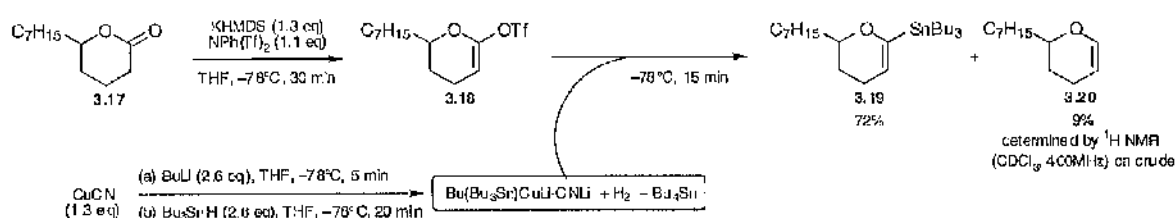


Scheme 3.6

While tributylstannane **3.15a** underwent quantitative transmetalation with 1 equivalent of BuLi to provide an α -alkoxyorganolithium species which could be trapped in 92% yield with CO₂, the trimethylstannane **3.15b** required 10 equivalent of BuLi in order to generate reasonable amounts of α -alkoxyorganolithium and still only provided 58% yield of the same trapped product **3.16**.

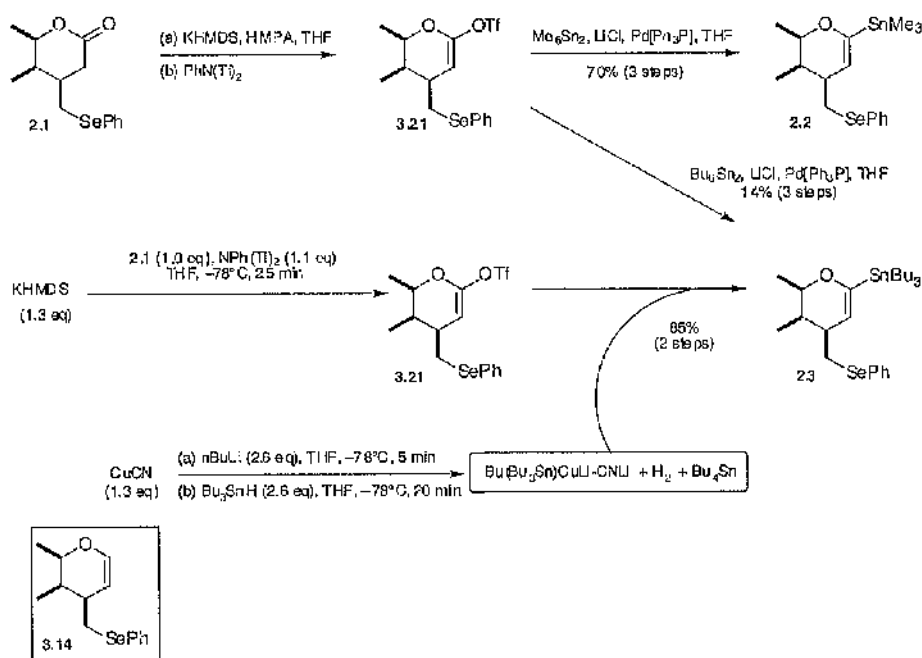
In the above example, it is likely that the difference in transmetalation chemistry of **3.15a** and **3.15b** is due to the difference in stabilities (ie relative acidity) of organolithiums involved. In fact, McGarvey has shown that the stability of organolithiums decreases in the order: R¹OCH₂Li > R¹OCH(R²)Li > MeLi > R¹OCR²R³Li > nBuLi > c-HexLi (R¹ = MOM).⁸⁸ Based on this ranking, Chong concluded that treatment of organostannane **3.15b** with BuLi should provide organolithium BOMOCH(Me)Li selectively rather than MeLi but with some degree of competition.

Although our lithiated dihydropyran **1.59** (scheme 3.5) should be more stable than a saturated α -alkoxyorganolithium analogue, synthesis of tributylstannane **2.3** was attempted. Unfortunately, using the same Pd(0) catalysed Stille-type procedure^{32, 75} with the bulky hexabutylditin occurred in very poor yield (14%). A more efficient synthesis was necessary. Fortunately, Tanya Wildman, a PhD student in the Kocienski group (1999-2002) was working on routes to vinylic stannanes from enol triflates using Lipshutz's mixed trialkylstannyl cyano cuprates⁸⁹ (unpublished results). Working on simple lactones such as **3.17** (scheme 3.7), she not only simplified and improved the preparation of enol triflates (e.g. **3.18**), but she also showed on simple lactones that reacting the corresponding enol triflates with (Bu₃Sn)Bu-CuLi-CNLi yields the corresponding vinyl tributylstannane (e.g. **3.19**) in good yield along with a little of the corresponding destannylated dihydropyran (e.g. **3.20**) (10-15%).



Scheme 3.7

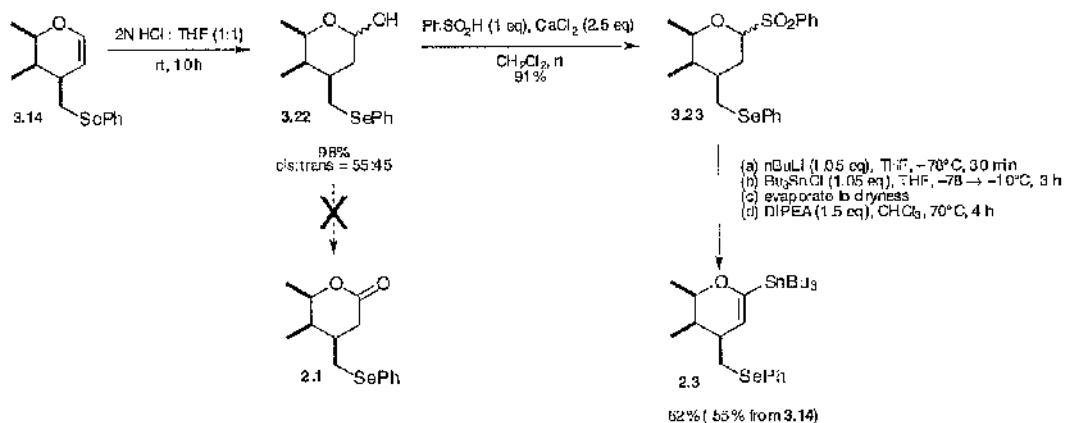
Although this methodology is being optimised, the tributylstannane **2.3** was obtained in good yield (62-85%) along with dihydropyran **3.14** (10-15%) as a byproduct (scheme 3.8) using Wildman's procedure.



Scheme 3.8

3.3 Recycling of dihydropyran **3.14**

As shown in scheme 3.5, dihydropyran **3.14** is produced as a byproduct in large quantities in our coupling reactions, since an excess of 2 equivalents of the precious stannanes **2.2** and **2.3** is used. Acid catalysed hydrolysis of dihydropyran **3.14** produced the corresponding lactols **3.22** in good yield (98%, dr = 55:45, in favour of the equatorial hydroxyl). Oxidation of lactols **3.22** to recover the previously described lactone **2.1** was foiled by competitive oxidation of the selenyl ether (scheme 3.9). Alternatively, lactols **3.22** were readily transformed into the sulfones **3.23** by reaction with phenylsulfonic acid in the presence of CaCl_2 . Deprotonation of the resulting sulfones, followed by direct condensation with tributylstannyl chloride and heating in chloroform containing Hünig's base, affords the vinylstannane **2.3** efficiently.^{90, 91}



Scheme 3.9

3.4 Conclusion

We have now in our hands a very efficient and economical synthetic route towards lactone **2.1**. Both stannanes **2.2** and **2.3**, precursors of the lithiated dihydropyran **1.59**, are now easily accessible from lactone **2.1**. Bearing in mind that our aim is to use the same metallated dihydropyran approach for every member of the pederin family, we are now ready to compare the reactivities of **2.2** and **2.3** in this reaction. Finally, the previously wasted dihydropyran byproduct **3.14** is now recycled in good yield, rendering the coupling reaction less wasteful.

Chapter 4 : Synthesis of Dihydropyranone 2.4

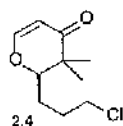
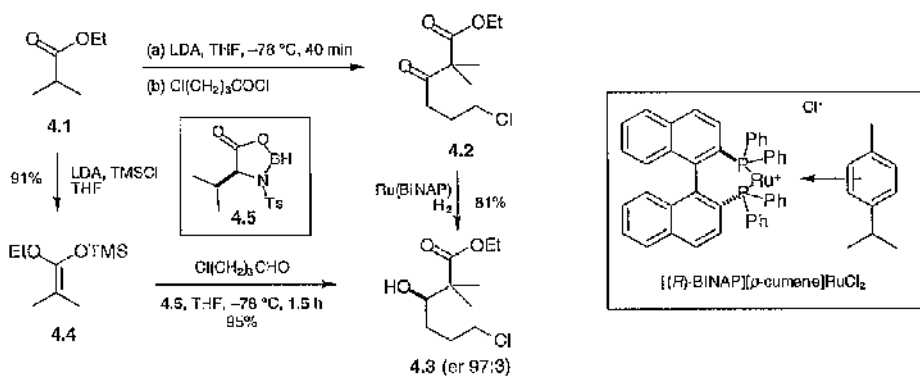


Figure 1

Dihydropyranone **2.4** is a critical intermediate in our synthetic strategy because it could, in principle, be converted to the simple monocyclic system of pederin as well as the more complex trioxadecalin ring system of the mycalamides, onnamides and theopederins. The 3-chloropropyl side chain in **2.4** also satisfied the need for an inert latent alkene which could be fashioned into any of the side chain variations of the pederin family. The optimised route⁷⁷ towards **2.4** is briefly described here

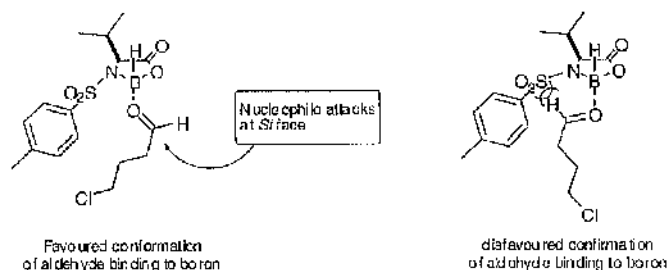
4.1 Creation of the C15-stereogenic centre

Dihydropyranone **2.4** harbours a single stereogenic centre at C-15 (mycalamide numbering) which was constructed efficiently by two different routes. In the first route, the lithium enolate prepared from ethyl isobutyrate was condensed with 4-chlorobutanoyl chloride to give the β -keto ester **4.2** in 93% yield (scheme 4.2). Noyori catalytic asymmetric hydrogenation of the β -keto ester **4.2** using [(*R*)-(+)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl] chloro (*p*-cymene) ruthenium chloride⁹²⁻⁹⁵ installed the requisite (*R*)-configured stereogenic centre in good yield and high enantiomeric ratio (97:3). The reaction worked well on a 50 mmol scale but on scaleup to 150 mmol, the reaction time was variable and occasionally it failed to go to completion. Moreover, the ruthenium catalyst was expensive and commercial supplies gave variable activity. Economy, scale, cost and reliability led us to an alternative synthesis of β -hydroxy ester **4.3** using an asymmetric directed aldol reaction mediated by the scalemic borane **4.5** according to the method of Kiyooka.^{96, 97} Although the Kiyooka method requires stoichiometric amounts of the borane **4.5**, it was easily prepared from cheap crystalline *N*-tosyl valine which was recovered in pure form after one recrystallisation in 90% yield. The directed aldol approach gave comparable yields and enantioselectivity and its ease of execution won our favour.



Scheme 4.2

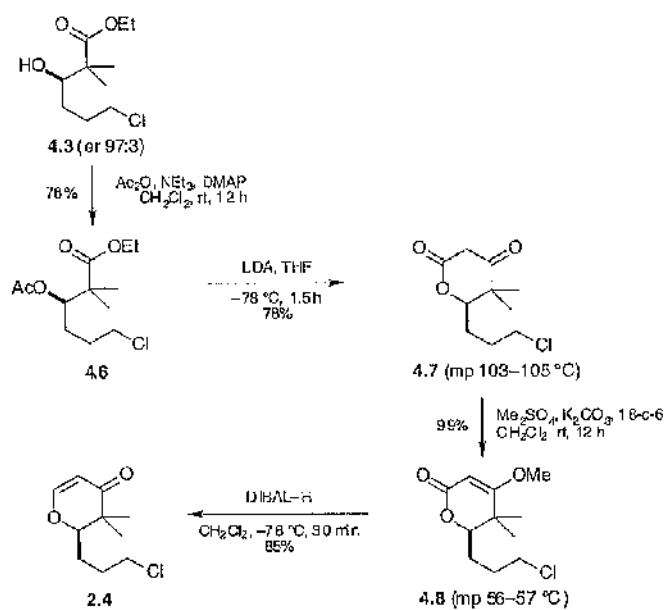
A conformation of **4.3** is represented diagrammatically in scheme 4.3 and is based on MM2 calculations performed by Kiyooka.⁹⁶ The isopropyl group governs the position of the sulfonamide group and together they define the co-ordination site for the aldehyde. The aldehyde co-ordinates with its *Si* face exposed to nucleophilic attack whilst co-ordination exposing the *Re* face of the aldehyde to nucleophilic attack is disfavoured due to steric repulsion.



Scheme 4.3

4.2 Conversion of β -hydroxy ester **4.3** to dihydropyranone **2.4**

To complete the synthesis, the ring was constructed by Dieckmann cyclisation of the acetate **4.6** to give the highly crystalline β -keto lactone **4.7** which could be easily obtained enantiopure by crystallisation (scheme 4.4). Simple *O*-methylation under phase transfer catalysed conditions afforded the crystalline enol ether **4.8**. Reduction of the remaining carbonyl with DIBAL-H returned the desired dihydropyranone **2.4** in 50-52% overall yield from ethyl isobutyrate. Note that none of the steps depicted in scheme 4.2 required column chromatography.



Scheme 4.4

Chapter 5 : Synthesis of Pederin

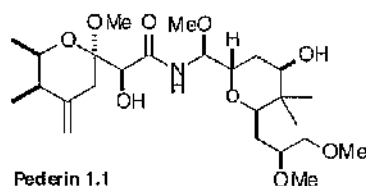


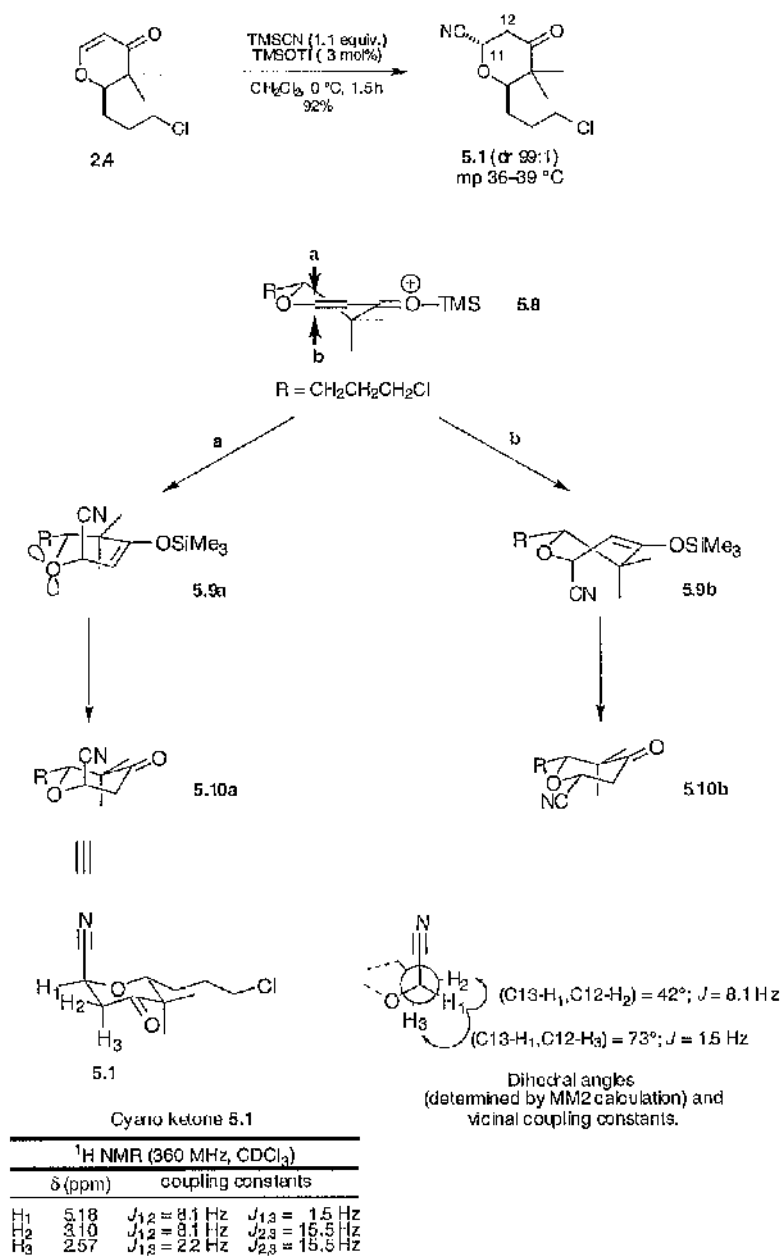
Figure 1

5.1 A formal synthesis of pederin

Kocienski and co-workers had already described a synthesis of pederin from the metallated dihydropyran **2.2** and the nitrile **2.5** which was expensive and impractical.³² The ready accessibility of dihydropyranone **2.4** on a large scale stimulated a fresh approach to the synthesis of nitrile **2.5** which is far more practical. Below, we summarise the conversion of dihydropyranone **2.4** to nitrile **2.5** which, together with our much improved synthesis of metallated dihydropyran **2.2** reported herein, represents a new formal total synthesis of pederin (schemes 5.2-5.4).

5.1.1 Construction of the C11 centre

Conjugate addition of trimethylsilyl cyanide to dihydropyranone **2.4** catalysed by TMSOTf gave the nitrile **5.1** as a single isomer in 92% yield. The pseudo axial disposition of the cyano group was evidenced by 360 MHz ¹H NMR spectroscopy (scheme 5.2) and is the result of both a double stereoelectronic control in the transition state leading to its formation. Thus, attack *via* path **a** proceeds through the flattened chair **5.9a** with additional stabilisation from the anti-periplanar lone pair adjacent to the newly formed bond, whilst attack *via* path **b** must proceed through the higher energy twist boat **5.9b** which also lacks a suitably aligned lone pair on the pyran oxygen. Prediction of the dihedral angles between C13-H and both C12 protons using MM2 calculation (Chem3D) as well as their coupling constants [¹H NMR spectroscopy (360 Hz, CDCl₃)] are in agreement with Karplus rules⁹⁸ (scheme 5.2). Occupation of the pseudo-axial position of the nitrile thereby confirmed the stereoselectivity.

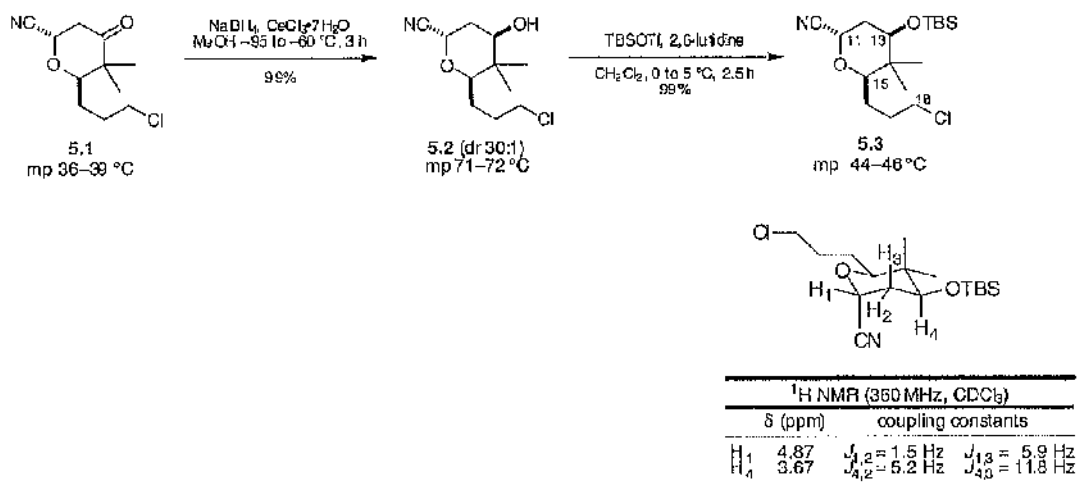


Scheme 5.2

5.1.2 Construction of the C13 stereogenic centre

Luche reduction⁹⁹ of the carbonyl group was diastereoselective affording a quantitative yield of diastereoisomeric alcohols (dr 30:1) from which the pure desired isomer **5.2** (scheme 5.3) could be obtained by crystallisation. In this reaction the stereoelectronic preference for axial attack was not subverted by the presence of the sterically undemanding axial nitrile group. Experimentally the best diastereoselectivity was obtained in the presence of CeCl_3 trihydrate at low temperature (-95°C) adding a large excess (4 eq) of sodium borohydride in one batch to the reaction mixture. However the diastereomeric ratio

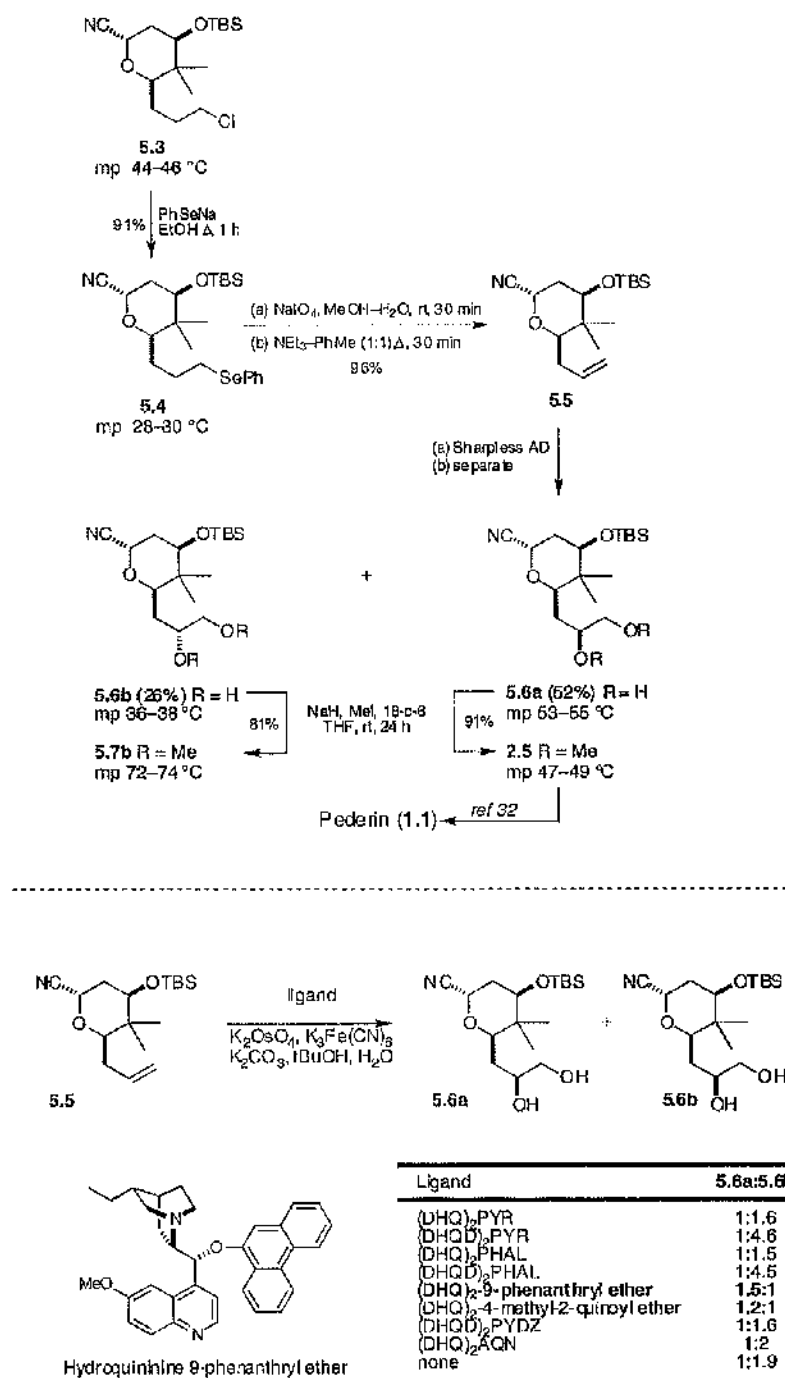
was determined by ^1H NMR (360 MHz, CDCl_3) spectroscopy by integration of signals (dd) of C11-H at $\delta = 4.91$ ppm (major) and 4.81 ppm (minor). The structure was confirmed after protection of the hydroxyl as its TBS ether by ^1H NMR (360 MHz, CDCl_3) as shown in scheme 5.3



Scheme 5.3

5.1.3 Construction of the side chain

After displacement of chloride with sodium phenylselenide, the alkene was generated by thermolysis of a selenoxide intermediate giving terminal alkene **5.5**. Experimentally, to avoid the side reactions or disproportionation reactions involving selenic acids¹⁰⁰, triethylamine was added to the organic extracts immediately after the work up. This method has become our method of choice and was used in every syn elimination of alkyl selenoxides in the following chapters. Several chiral ligands for the Sharpless asymmetric dihydroxylation of olefin **5.5** were screened [(DHQD)₂PYR¹⁰¹, (DHQD)₂PYR, (DHQ)₂PHAL¹⁰², (DHQD)₂PHAL¹⁰³, (DHQ)₂9-phenanthryl ether¹⁰⁴, (DHQ)₂-4-methyl-2-quinoyl ether¹⁰⁴, (DHQD)₂PYDZ¹⁰⁵ and (DHQ)₂AQN¹⁰⁶) but the diastereoselectivity was modest at best (scheme 5.4). The diastereomeric ratio was determined by integration of the signal (dd) derived from C11-H in the ^1H NMR spectrum at $\delta = 4.90$ (**5.6b**) ppm and $\delta = 4.86$ (**5.6a**) ppm and the stereoconfiguration was confirmed at the next step.



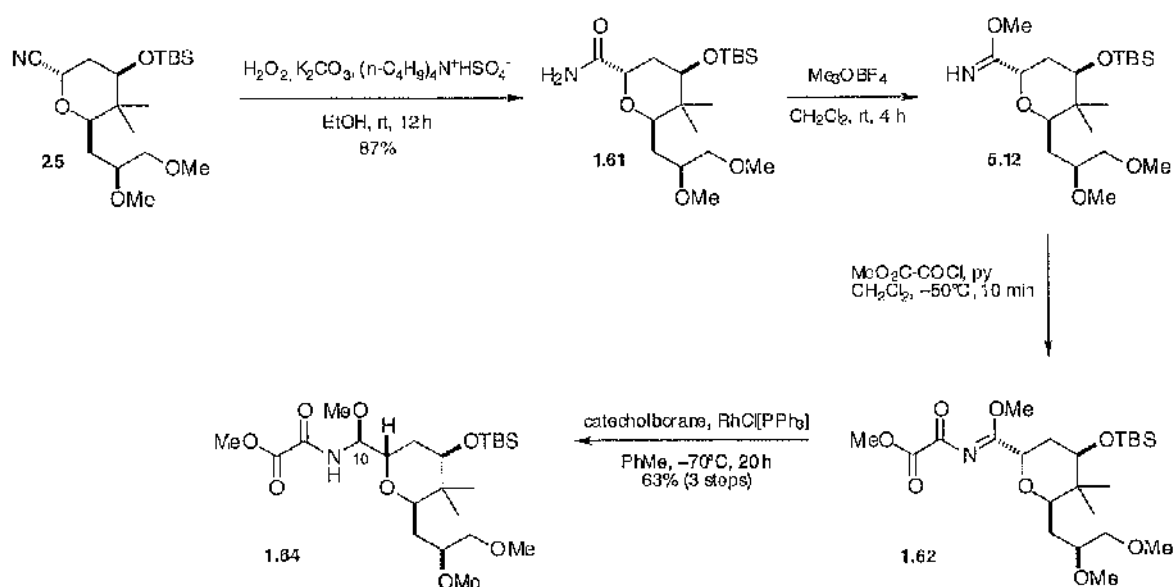
Scheme 5.4

The desired (17*S*)-diol **5.6a** was then methylated to give the crystalline nitrile **2.5** which was converted to pederin as described previously.³²

5.2 Completion of the right fragment of pederin

From the nitrile **2.5**, pederin was synthesised as described previously³² (schemes 5.5 and 5.6), with comparable results. This route deserves further comments since a similar

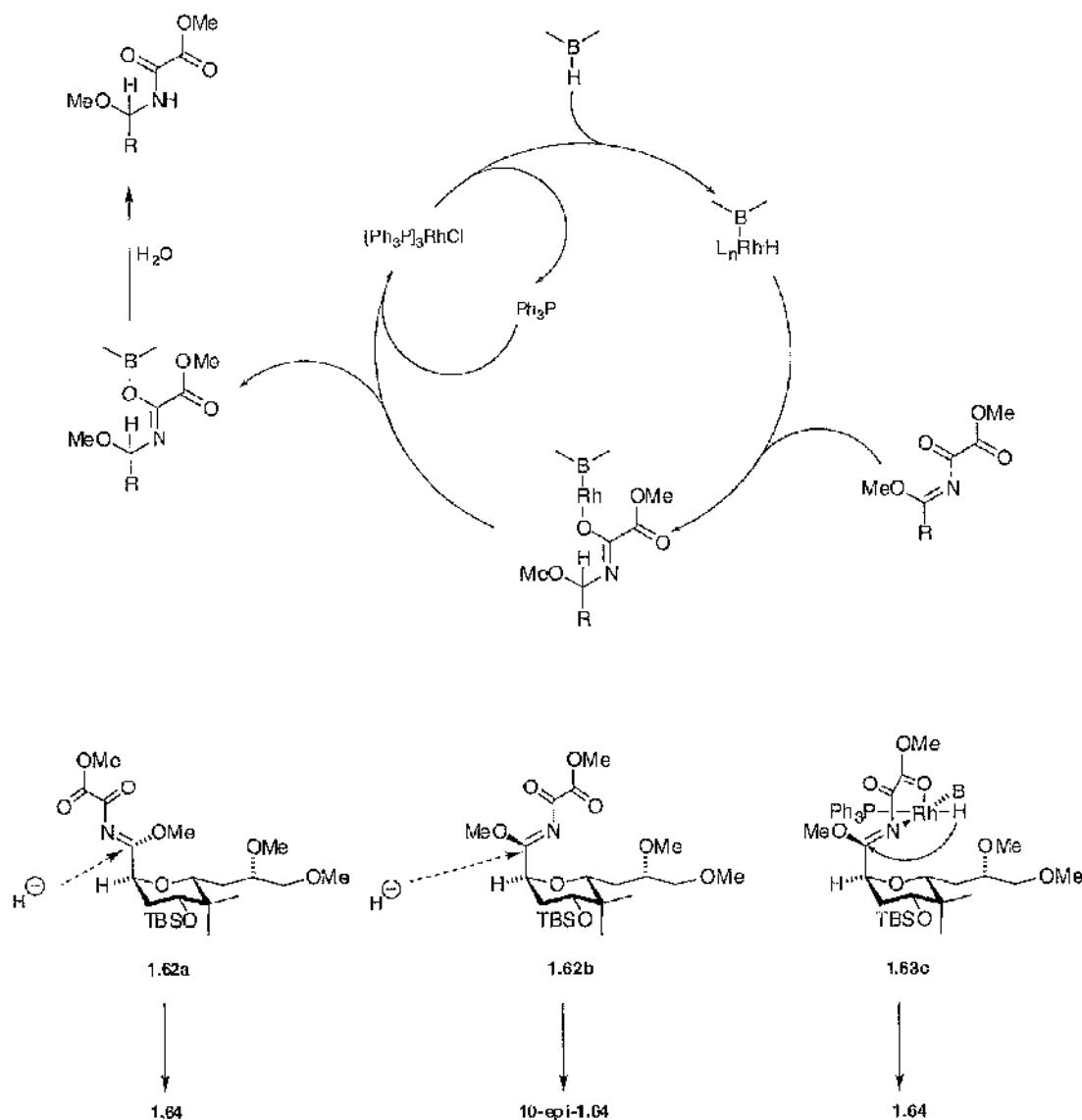
strategy is applied to the synthesis of analogues of pederin (chapter 7). Nitrile **2.5** was converted to fragment **1.64** in four steps. Both imidate **5.12** and ester **1.62** were prone to hydrolysis and the yield was maximised by proceeding to **1.64** quickly with minimal purification of intermediates. Rhodium-mediated reduction of the *N*-acylimidate **1.62** proceeded with high stereoselectivity yielding **1.64** with 30:1 selectivity after column chromatography (scheme 5.5). Integration of the signals (dd) arising from C10-H at $\delta = 5.21$ ppm (major) and $\delta = 5.12$ ppm (minor) determined the ratio of the diastereomers.



Scheme 5.5

A mechanism for the reduction involving a rhodium-catalysed 1,4-hydroboration reaction is proposed in scheme 5.6. Previous studies have demonstrated that high levels of stereocontrol were achieved in the formation of the unwanted diastereomer 10-*epi*-**1.64** in accord with a preferential attack on rotamer **1.62b** from the least hindered face of the *N*-acylimidate function. Consequently, stereoselective reduction in the desired sense requires some means for enhancing the population of rotamer **1.62a** or, alternatively, a means for delivering hydride from the more hindered face of **1.62b**. The rhodium complex **1.63c** in which the *N*-acylimidate side chain serves as a bidentate ligand in the rhodium complex derived from oxidative addition of Rh(I) to the borane. In this complex, the triphenylphosphine ligand very effectively shields the *Si* face of the *N*-acylimidate thereby directing reduction to the desired *Re* face. According to models, the corresponding complex from rotamer **1.62a** suffers from severe steric congestion with the TBS protecting group at C13. It has been shown that the role of the protecting group in ensuring preferential formation of complex **1.63c** is crucial since the reduction of the *N*-acylimidate

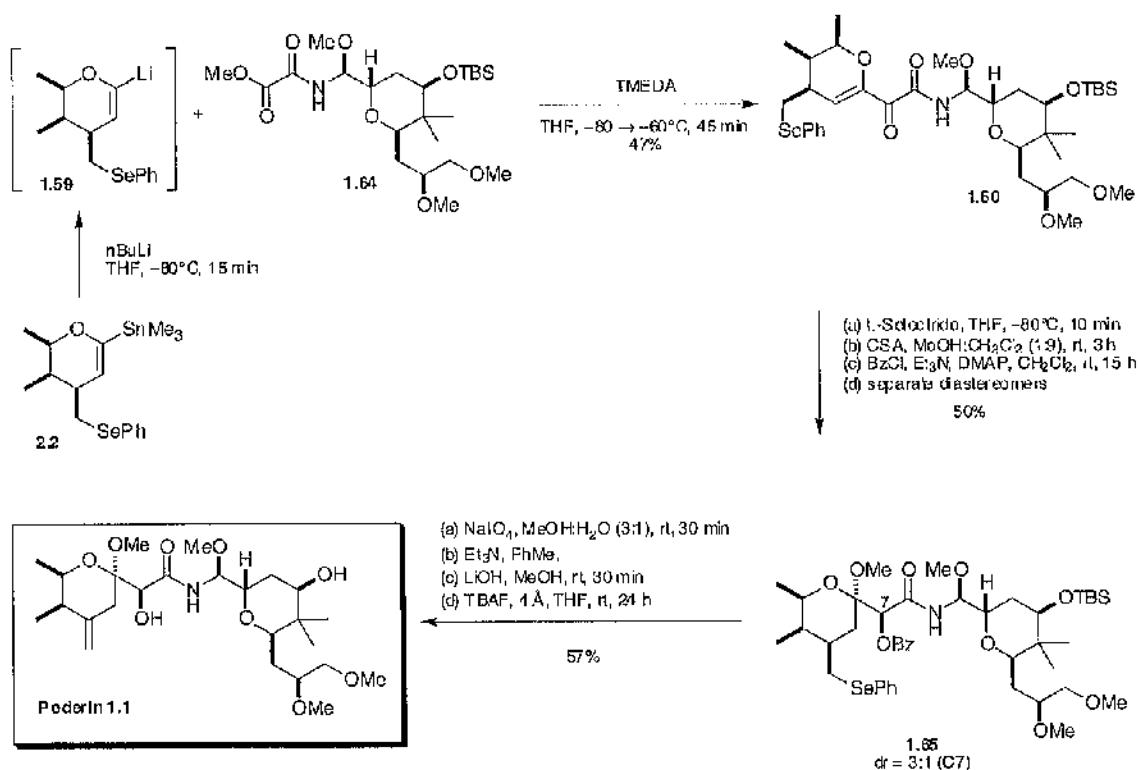
bearing an *O*-benzoyl function at the C13 was much less diastereoselective (3:2 vs >10:1).³²



5.3 Coupling and completion

Transmetalation of the trimethylstannane **2.2** and reaction with ester **1.64** in the presence of TMEDA at low temperature gave adduct **1.60** in modest yield (47%) as shown in scheme 5.7. With the bulk of the pederin skeleton now constructed, completion of the synthesis required the introduction of the two adjacent stereogenic centres at C6 and C7 as well as a few functional group transformations. The reduction of the carbonyl at C7 required the bulky reducing agent $\text{LiBH}(\text{s-Bu})_3$ to yield the corresponding alcohols with modest stereoselectivity (3:1). The diastereomeric ratio was determined by integration of

the signal (s) derived from C7-H in the ^1H NMR spectrum (400 MHz, CDCl_3) at $\delta = 5.53$ (major) ppm and $\delta = 5.55$ (minor) ppm. Addition of methanol in the presence of camphorsulfonic acid followed by the protection of the hydroxyl at C7 yielded the desired compound **1.65** as a mixture of diastereoisomers **1.65a,b**. Separation of **1.65a** and **1.65b** was accomplished easily by preparative thin layer chromatography. Pederin was finally obtained by elimination of the selenoxide, hydrolysis of the benzoate, and TBS deprotection. The ^1H NMR and ^{13}C NMR of pederin **1.1** were recorded in C_6D_6 to avoid decomposition of this acid-sensitive compound that had been previously reported³² using CDCl_3 as the NMR solvent.



Scheme 5.7

Chapter 6 : Total synthesis of Mycalamide B and 17-*epi*-Mycalamide B

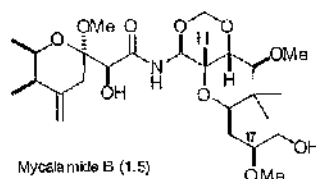


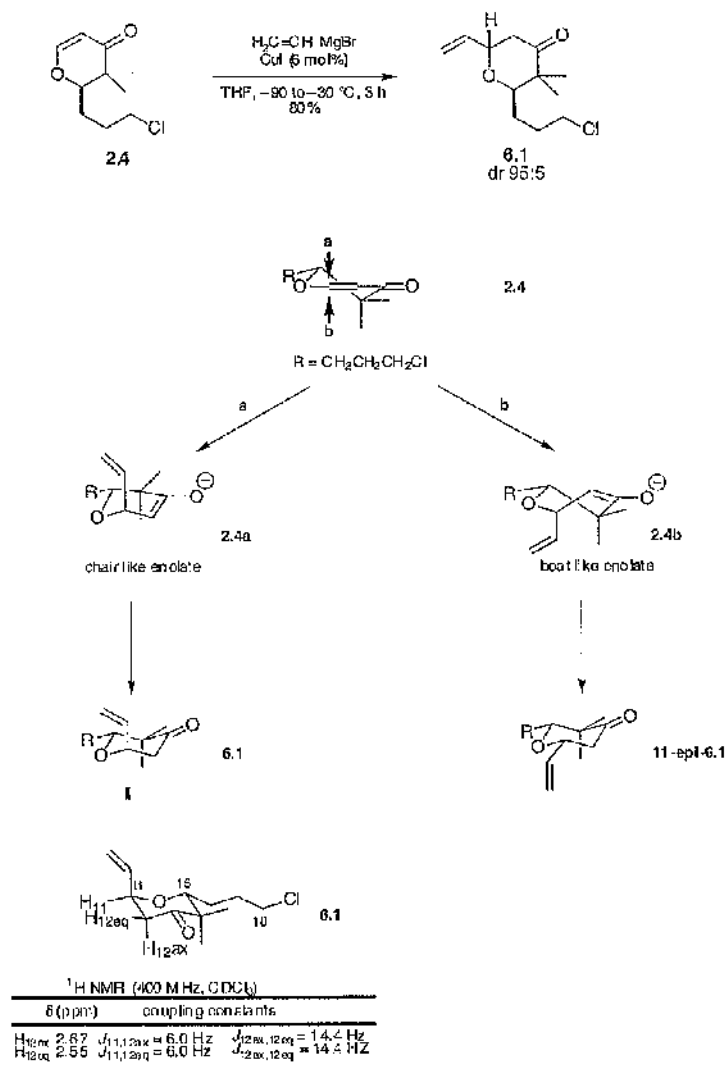
Figure 6.1

6.1 Construction of the 1,3-dioxane ring

Construction of the 1,3-dioxane ring required a 3-stage sequence of 7 steps comprising appendage of a 2-carbon unit to the dihydropyranone; two oxidations at C10 and C12; and finally ring closure.

6.1.1 Construction of the C11-centre

The first stage was accomplished in high yield (80%) and high diastereoselectivity (dr 95:5) by Cu(I)-catalysed conjugate addition of vinylmagnesium bromide to dihydropyranone **2.4** as shown in scheme 6.2. The 1,4-addition of a cuprate or organomagnesium reagent to an α,β -unsaturated ketone is an irreversible process¹⁰⁷. As a consequence, the products should be governed by kinetic control¹⁰⁷, and the stereoselectivity can be explained by the relative energies of the transition states. Indeed, attack *via* path **a** proceeds through a chair like enolate **2.4a** whilst attack *via* path **b** must proceed through the higher energy boat like enolate **2.4b**. The stereochemistry at the C11 centre was confirmed by ¹H NMR spectroscopy with the coupling constants between both C12 protons and C11-H being 6.0 Hz (scheme 6.2).

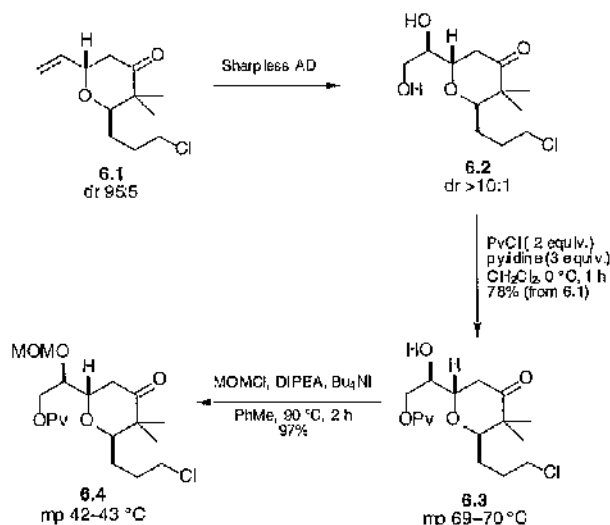


Scheme 6.2

6.1.2 Construction of the C10-centre

Attempts to launch the second stage by substrate controlled dihydroxylation gave poor diastereocontrol [10(*R*):10(*S*) 2:3] so the task was accomplished using the Sharpless asymmetric dihydroxylation (scheme 6.3).¹⁰⁸ Using 20 mg of substrate, several ligand systems were screened but the diastereoselectivity was modest at best: AD-mix-α [10(*S*):10(*R*) 1:2], AD-mix-β (2:1), (DHQ)₂PYR¹⁰¹ (1:3.5), (DHQD)₂PYR (2.6:1), DHQD-PYDZ¹⁰⁵ (1.3:1) and DHQ 4-methyl-2-quinolyl ether¹⁰⁴ (1:7.5). Best results were obtained with DHQ 9-phenanthryl ether¹⁰⁴ which gave a 75% yield of diols with dr > 10:1 in favour of the desired 10(*R*) derivative **6.2**. The ratio between the two diastereoisomers was determined by ¹H NMR spectroscopic analysis by integration of the signals derived from C14-Me [¹H NMR (360 MHz, CDCl₃) : δ = 1.28 ppm (minor) and 1.26 ppm (major)]. The diols were inseparable but the corresponding monopivalates were separable

by simple crystallisation from ether–hexanes to afford pure **6.3** in 78% yield. The remaining hydroxyl group was converted to its crystalline MOM ether **6.4** which not only served as a protecting group, but also as an essential participant in the final ring construction.



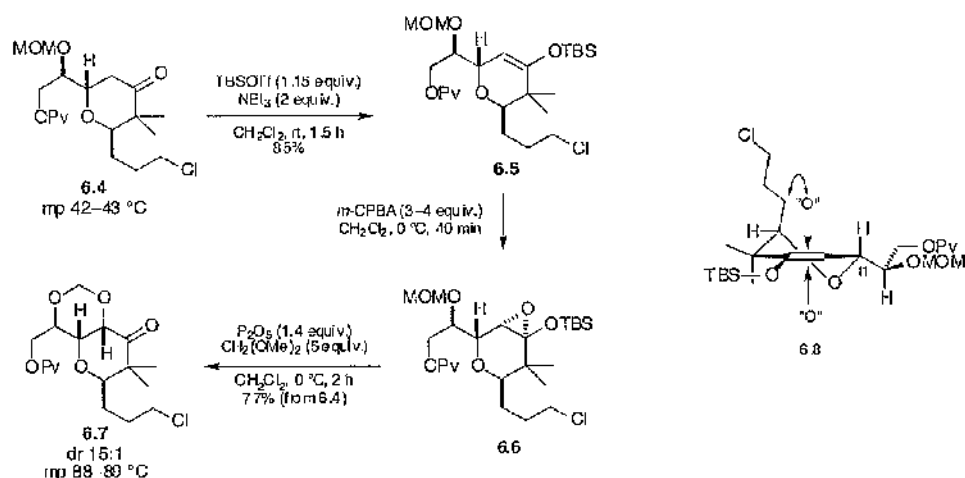
Scheme 6.3

6.1.3 Construction of the trioxadecalin ring

The second oxidation was accomplished by simple epoxidation of the enol silane derivative **6.5** prepared from ketone **6.4** and TBSOTf. Two aspects of the conversion **6.5** to **6.6** are noteworthy. First, the epoxidation was highly diastereoselective giving virtually a single diastereoisomer with the desired stereochemistry at C12 (scheme 6.4). Secondly, the oxirane **6.6** was surprisingly stable—e.g., it could be purified by silica gel chromatography without detriment though in practice, the crude product was generally used in the next step.

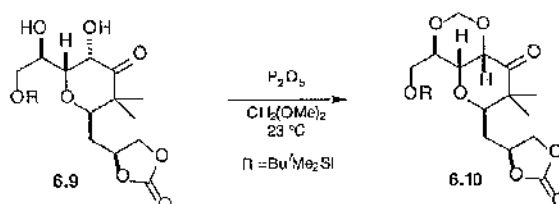
The very favourable stereochemistry of the epoxidation of enol silane **6.5** deserves comment. We had originally expected difficulty with this step because it would appear that epoxidation was required from the same face of the ring as the bulky and branched side chain at C11. However, the C11 side chain can occupy a pseudo-equatorial position in the half chair conformation as shown in Scheme 6.8 in which it offers comparatively little steric impediment to the approach of the oxidant compared with the pseudo-axial 3-chloropropyl side chain at C15. Indeed, an MM2 calculation (Chem3D) predicts that the 3-chloropropyl side chain protrudes over the ring somewhat thereby exacerbating its steric effect hence forcing the epoxidation to take place as shown. The favourable stereochemistry could be ascribed to tethered delivery of the *m*-chloroperbenzoic acid via a

hydrogen-bonded intermediate but the same favourable stereochemistry was also obtained with dimethyldioxirane in which hydrogen bonding is precluded.



Scheme 6.4

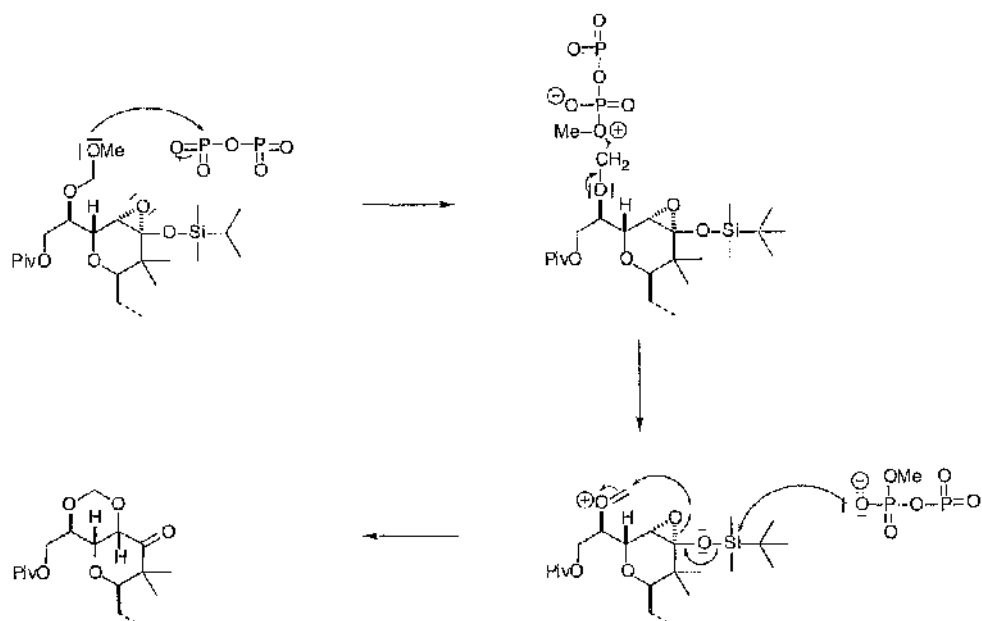
During a synthesis of the trioxadecalin nucleus of mycalamide A, Roush⁵⁰ had prepared the methylene acetal in **6.10** (Scheme 6.5) by adding phosphorus pentoxide to a solution of diol **6.9** in dimethoxymethane according to literature precedent.



Scheme 6.5

We found that the methylene acetal could be constructed directly by adding the oxirane **6.1** to a solution of phosphorus pentoxide in dichloromethane containing a large excess of dimethoxymethane at 0 °C. An overall yield of 77% was obtained for the three steps from ketone **6.4** to methylene acetal **6.7** with a diastereoselectivity of 15:1. The methylene acetal could be obtained as a single diastereoisomer by simple crystallisation from ether–hexanes.

A possible mechanism of the formation of the ketone **6.7** is given in scheme 6.6.



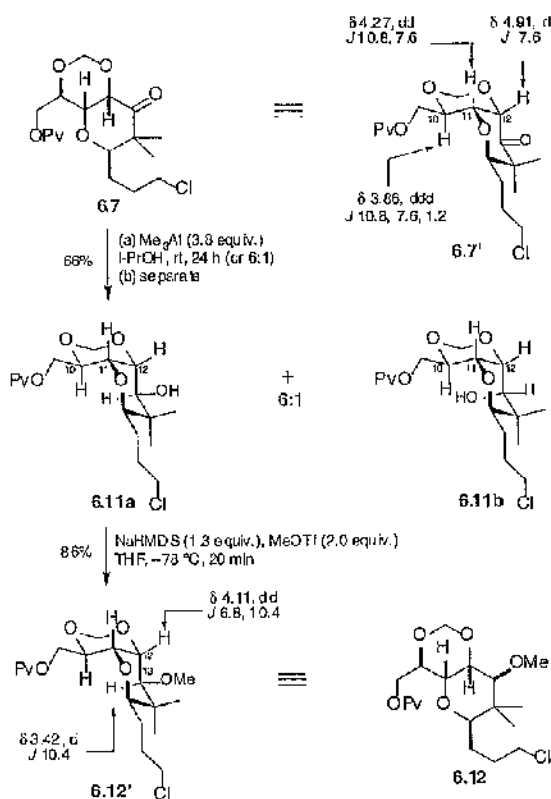
Scheme 6.6

However, experimentally, both a lower yield (70%) and lower diastereoselectivity (ca 8:1) was obtained when the phosphorus pentoxide was added to a solution of the oxirane in a mixture of dimethoxymethane in dichloromethane. Thus another plausible mechanism for this reaction is given in scheme 6.7.



The reduction of the C13 carbonyl which introduced the single remaining stereogenic centre on the ring was thwarted by poor stereoselectivity (scheme 6.8). The most favourable ratio of **6.11a**:**6.11b** (1:1) was obtained with KBH_4 and $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ in MeOH at -90 to -20 °C ; all other variants gave mixtures rich in **6.11b**. $\text{BH}_3 \cdot \text{THF}$ and $\text{LiBH}(\text{s-Bu})_3$ gave exclusively **6.11b**; Rhodium-catalysed hydrosilylation gave predominantly **6.11b**. Dissolving metal reduction (Na, SnI_2) gave decomposition but Mg in MeOH gave a 1:1 mixture with competing reduction of the chloride. Fortunately, the diastereoisomeric alcohols were easily separable thereby allowing a recycling process. A reason for the poor stereoselectivity can be gleaned from the ground state conformation of

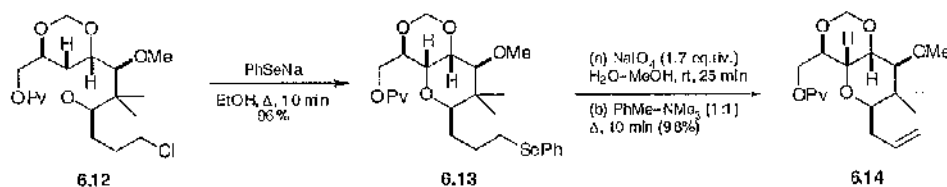
the ketone **6.7**: formation of the desired stereoisomer **6.11a** requires delivery of hydride from the more hindered concavity of the *cis*-fused trioxadecalin system. This recalcitrant reduction was the greatest obstacle to progress until a simple, convenient and effective solution to the problem was found in the form of a modified Meerwein–Ponndorf–Verley reduction. Thus treatment of ketone **6.7** at room temperature with a reagent prepared by reaction of isopropanol with trimethylaluminium (3.8 equiv.) gave a mixture of **6.11a** and **6.11b** in 66% yield with a dr of 6:1 in favour of **6.11a**. Starting ketone **6.7** was also recovered (28%) making the yield based on recovered starting material 92%. The reversible nature of the Meerwein–Ponndorf–Verley reduction is well known to afford the thermodynamic alcohol.¹⁰⁹ Evidence that **6.11a** is the thermodynamic product comes from two observations. First, the dr of the reaction was a function of time with the mol fraction of **6.11a** increasing with time. Secondly, subjection of the pure axial alcohol **6.11b** to the reaction conditions led to isomerisation. Attempts to drive the reduction to completion by removing the acetone at elevated temperature led to diminished dr. *O*-Methylation of **6.11a** gave a methyl ether **6.12** whose stereochemistry was assigned based on the large coupling constant $J_{12,13}$ 10.4 Hz for $C_{13}H$ consistent with a *trans*-diaxial disposition of the vicinal hydrogens as indicated in structure **6.12'**.



Scheme 6.8

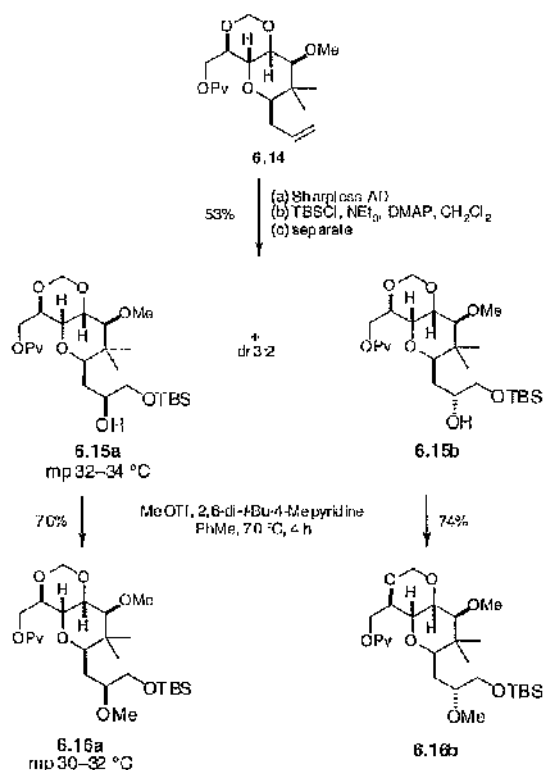
6.3 Installation of the C15 side chain

The C15 side chain is the principal seat of structural variation in the pederin family and our route was designed to access as many members of the pederin family and their analogues as possible. The chloropropyl side chain was introduced at the outset because it offered opportunities for nucleophilic substitution or elimination and thence a rich vein of transformations. For the synthesis of mycalamide B, we required an elimination reaction. However, neither the chloride nor iodide would eliminate without severe decomposition. Therefore, we were forced to adopt a regrettable 3 step sequence involving substitution by phenylselenide anion to give phenylseleno ether **13** (scheme 6.9) whence thermolysis of the corresponding selenoxide¹¹⁰ afforded the desired alkene **6.14** in excellent overall yield (94%) for the 3-step sequence from **6.12**.



Scheme 6.9

To complete the elaboration of the C15 side chain (scheme 6.10) we performed a Sharpless asymmetric dihydroxylation as Hong and Kishi³⁴ had done before us. The diastereoselectivity was poor giving a mixture of diols (dr 3:2) which was difficult to separate but the corresponding mono-TBS ethers were separable by chromatography and gave the desired alcohol **6.15a** as a crystalline solid together with its C17 epimer **6.15b**. Both compounds were converted to their respective methyl ethers **6.16a** and **6.16b**. As before the whole gamut of standard ligands used for the Sharpless asymmetric dihydroxylation was surveyed in the search for improved diastereoselectivity but to no avail. Once again DHQ 9-phenanthryl ether¹⁰⁴ maximised the desired diastereoisomer but the highest diastereoselectivity (9:1) was obtained with (DHQD)₂PYR¹⁰¹ with the major isomer being the unwanted C17 epimer **6.16a**. The stereochemistry of the desired alcohol **6.16a** was established by X-ray analysis of a subsequent advanced intermediate (see below).

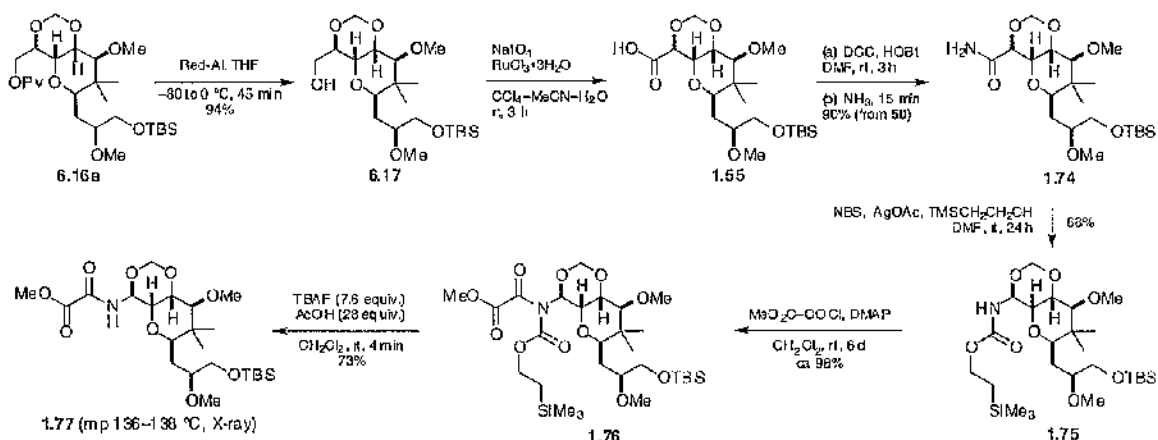


Scheme 6.10

6.4 Installation of the *N*-acyl aminal function

The last remaining task in the synthesis of the trioxadecalin fragment entailed the introduction of the *N*-acyl aminal function. The acid- and base-lability of the *N*-acyl aminal together with the threat of isomerisation under basic conditions demanded a mild, and reliable route. Our optimised solution is depicted in scheme 6.11. Reductive cleavage of the pivalate ester **6.16a** followed by oxidation of the primary alcohol **6.17** using the Sharpless protocol¹¹¹ gave the carboxylic acid **1.55** which was converted to the corresponding primary amide **1.74** using standard procedures. A classical Hofmann rearrangement using Ag(I)-assisted rearrangement¹¹² of the *N*-bromoamide derivative occurred at room temperature with clean retention of configuration to give an isocyanate intermediate which was trapped by 2-(trimethylsilyl)ethanol to give the carbamate **1.75** in 79% overall yield from the alcohol **6.17**. Alternatively, the Hofmann rearrangement could be induced by reaction of amide **1.74** with 1,1-bis(trifluoroacetoxy)iodobenzene^{113, 114} but the yield was slightly lower (73%). The Curtius rearrangement of an acyl azide derived from acid **1.55** is a well-precedented route to the carbamate **1.75** (see below) which we also evaluated. However, the elevated temperatures (70 °C) required for the rearrangement resulted in decomposition with an overall reduction in yield to 56% at best with typical yields being more like 40%. Attempts to reduce the temperature by employing the

photochemical variant of the Curtius rearrangement were rewarded with a multiplicity of products and so the route was abandoned in favour of the Hofmann rearrangement.



Scheme 6.11

The remaining 2-carbon fragment was installed by reaction of carbamate **1.75** with methyl oxalyl chloride in the presence of DMAP⁵⁸ to yield the imide derivative **1.76**. Although the reaction required 6 days to go to completion, the yield of the imide was excellent (98%). To complete the sequence, the urethane function was cleaved using TBAF buffered with acetic acid to give the crystalline trioxadecalin fragment **1.77** in 73% yield. In the absence of acetic acid, the primary TBS group was also partially cleaved. The structure and relative stereochemistry of **1.77** was firmly established by X-ray crystallography (Fig. 6.1).

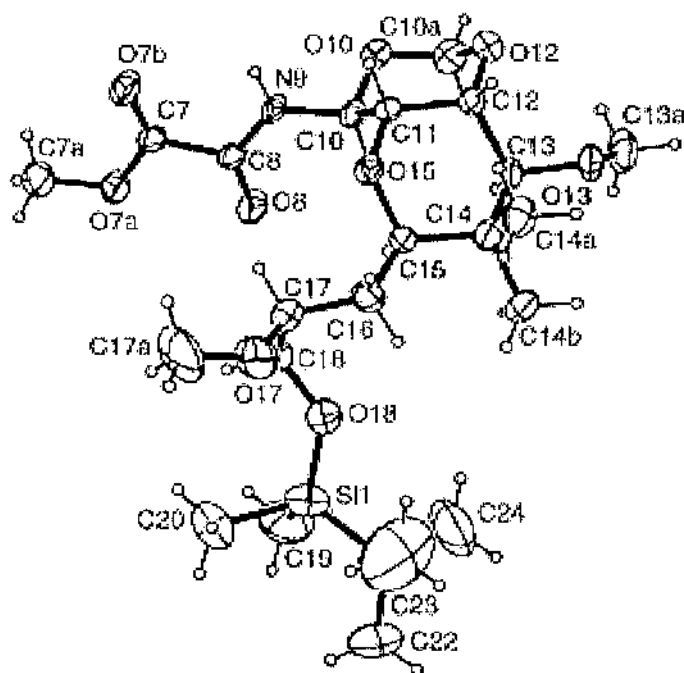
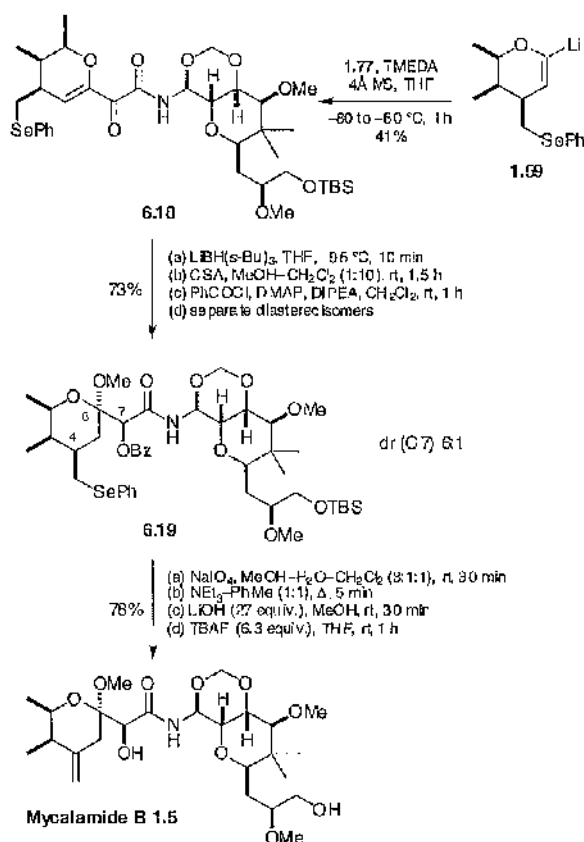


Fig. 6.1 X-ray crystal structure of compound **1.77** showing the atom numbering and 20% probability ellipsoids for non-hydrogen atoms.

6.5 Coupling and completion of the synthesis of mycalamide B

The principal task required to complete the synthesis of mycalamide B was the construction of the *N*-acyl aminal bridge linking the two ring systems by deploying the same linkage strategy as previously described. Thus addition of the trioxadecalin fragment **1.77** (scheme 6.12) to a mixture of the lithiated dihydropyran **1.59** (2.7 equiv.) (derived from the trimethylstannane **2.2**) and *N,N,N',N'*-tetramethylethylenediamine (TMEDA) at low temperature gave the adduct **6.18** in 41% yield.



Scheme 6.12

The acyldihydropyran adduct **6.18** harboured the entire skeleton of mycalamide B and completion of the synthesis now only required some functional group manipulations which began with reduction of the keto group with $\text{LiBH}(\text{s-Bu})_3$. The crude product underwent acid-catalysed addition of MeOH to the dihydropyran and the remaining hydroxyl function was acylated with benzoyl chloride. ^1H NMR spectroscopic analysis of the crude reaction mixture revealed two diastereoisomeric benzoates (dr 6:1) which were separated by chromatography to give the pure benzoate **6.19** in 73% overall yield from **6.18**. Two stereogenic centres at C6 and C7 were created in the forgoing transformations but the detection of only two isomers at C7 indicates that addition of MeOH had occurred with very high diastereoselectivity. Brief thermolysis of the selenoxide derived from oxidation of phenylselenanyl ether **6.18** installed the hypersensitive methylene function at C4. Finally, hydrolysis of the benzoate ester with lithium hydroxide followed by cleavage of the primary TBS ether with TBAF produced mycalamide B in 78% overall yield from **6.18**. By using identical procedures, 17-*epi*-mycalamide B was prepared from **6.16b** with comparable overall efficiency. The ^1H and ^{13}C NMR spectroscopic data recorded on natural and synthetic mycalamide B together with the data for the 17-*epi* diastereoisomer are summarised in Table 6.1. Data for the synthetic material is also given in C_6D_6 owing to the slow deterioration of the synthetic material in CDCl_3 .

Table 6.1. ¹H and ¹³C NMR data for natural and synthetic mycalamide B derivatives.

Position	Mycalamide B natural (CDCl ₃)		Mycalamide B synthetic (CDCl ₃)		Mycalamide B synthetic (C ₆ D ₆)		17-api-Mycalamide B synthetic (C ₆ D ₆)	
	¹ H (J, Hz)	¹³ C	¹ H (J, Hz)	¹³ C	¹ H (J, Hz)	¹³ C	¹ H (J, Hz)	¹³ C
2	4.22, dq (2.8, 6.6)	69.64	4.04, dq (2.6, 6.5)	—	3.80, dq (1.8, 5.6)	68.1	3.82, dq (2.6, 6.6)	68.0
2-Me	1.20, d (6.6)	17.93	1.21, d (6.6)	—	0.81, d (6.6)	16.5	0.81, d (6.6)	16.5
3	2.24, dq (2.4, 6.9)	41.27	2.28, dq (2.8, 7.1)	—	1.86, dq (1.7, 7.0)	40.4	1.88, dq (2.6, 7.1)	40.3
3-Me	1.01, d (7.1)	12.13	1.02, d (7.2)	—	0.92, d (7.0)	11	0.90, d (7.1)	12.1
4	—	145.10	—	—	—	144.6	—	145.0
4=CH ₂	4.85, dd (2.0, 2.0)	111.02	4.86, br s	—	4.71, dd (1.8, 1.8)	109.6	4.75-4.70, m	109.4
	4.72, dd (1.9, 1.9)	—	4.73, br s	—	4.65, dd (1.9, 1.9)	—	4.75-4.70, m	—
5	2.22, ddd (2.0, 2.0, 13.5)	86.43	2.24, dm (13.9)	—	2.40, dd (1.8, 14.0)	32.9	2.42, br d (13.9)	33.0
	2.36, d (13.9)	—	2.37, d (14.0)	—	2.60, d (14.0)	—	2.60, d (13.0)	—
6	—	99.95	—	—	—	99.2	—	99.1
6-OMe	3.29, s	48.57	3.3, s	—	3.15, s	47	3.21, s	47.1
7	4.29, s	71.73	4.29, d (2.0)	—	4.16, s	70.7 or 70.9	4.17, s	71.1
7-OH	—	—	3.88, d (2.1)	—	4.07 (br s)	—	4.17, s	—
8	—	171.88	—	—	—	171.1	—	171.1
NH	7.54, br d (10.0)	—	7.52, d (9.6)	—	7.58, d (9.8)	—	7.46, d (9.9)	—
10	5.79, dd (9.7, 9.7)	73.90	5.81, dd (9.6, 9.6)	—	5.83, d (9.9)	72.8	5.94, d (9.9)	72.6
10-O-CH ₃	5.12 (7.0)	96.49	5.12, d (7.0)	—	4.56, d (7.0)	85.1	4.57, d (6.9)	85.0
	4.84 (8.9)	—	4.86, d (6.7)	—	4.53, d (6.9)	—	4.54, d (6.9)	—
11	3.79 (6.7, 9.7)	70.94 (br)	3.79, dd (6.8, 9.6)	—	3.69, dd (7.0, 10.0)	70.7 or 70.9	3.65, dd (7.1, 9.7)	70.1
12	4.21 (6.7, 10.4)	74.44	4.22, dd (6.8, 10.2)	—	4.24, dd (7.0, 10.6)	73.9	4.23, dd (6.9, 10.2)	73.8
13	3.44 (10.5)	79.27	3.44, d (10.4)	—	2.94, d (10.5)	77.5 or 77.7	2.96, d (10.4)	77.6
13-OMe	3.55, s	61.78	3.56, s	—	3.22, s	60	3.32, s	60.0
14	—	41.47	—	—	—	40.3	—	40.1
14-Me ₂ C=	0.97, s	23.13	0.99, s	—	0.80, s	21.5	0.83, s	21.7
14-Me ₂ C=	0.85, s	13.32 (br)	0.87, s	—	0.76, s	11.9	0.77, s	12.1
15	3.41 (3.3, 8.8)	76.46	3.46-3.40, m	—	3.40, dd (5.0, 6.1)	74.4	3.51, d (9.3)	75.9
16	1.55, m	29.83	1.58-1.52, m	—	1.59-1.53, m	29.3	1.65, dd (8.2, 14.8)	31.5
	1.55, m	—	1.58-1.52, m	—	1.59-1.53, m	—	1.27, ridd (2.8, 10.0, 14.6)	—
17	3.2, m	78.84	3.23-3.16, m	—	3.33-3.28, m	77.5 or 77.7	3.27-3.18, m	78.3
17-OMe	3.24, s	56.64	3.25, s	—	3.03, s	55.2	3.06, s	55.6
18	3.65 (3.3, 11.9)	63.48	3.70-3.63, m	—	3.85-3.77, m	62.6	3.61-3.55, m	62.6
	3.47 (5.7, 11.9)	—	3.62-3.46, m	—	3.74-3.68, m	—	3.61-3.55, m	—
18-OH	—	—	—	—	2.33, br s	—	1.50, br s	—

Chapter 7 : Synthesis of Pederin analogues 2.8, 2.9 and 2.10

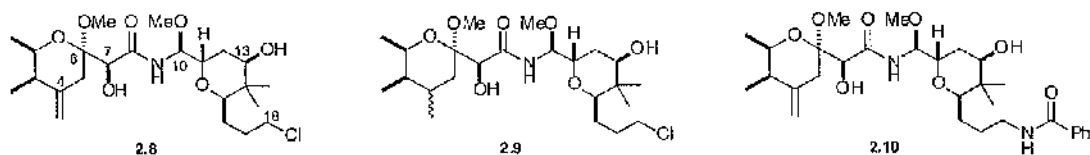


Figure 7.1

7.1 Choice of analogues

7.1.1 Summary of the SAR data of the pederin family

As described in chapter 1, sec. 3, structure activity studies on the pederin family of antitumour agents established that the *N*-acyl aminal bridge is the pharmacophore. The homoallylic acetal array encompassing C4–C6 which is responsible for the acid lability of the natural products as well as their vesicant effects, is not necessary for antitumour or antiviral activity. The C6 acetal function contributes to the high activity of the natural products though studies of simpler analogue reveal that it is not essential. The presence of a free hydroxyl group at C7 with the (*S*)-configuration is important for high activity. The configuration of the aminal centre is also very important with the (*S*)-configuration at C10 being significantly more active as an antitumour agent than the (*R*)-epimer; however, compounds with the (*R*)-configuration at C10 remain potent antiviral agents. The complex trioxadecalin ring system characteristic of the mycalamides, onnamides and theopederins is not essential for high activity since pederin, with its simpler monocyclic right half, is one of the most active of the natural products followed closely by 18-*O*-methyl-mycalamide B, a simple synthetic derivative of natural mycalamide B. Finally, the side chain at C15 tolerates considerable variation with comparatively little impact on activity. A summary of the SAR data is given in figure 7.2.

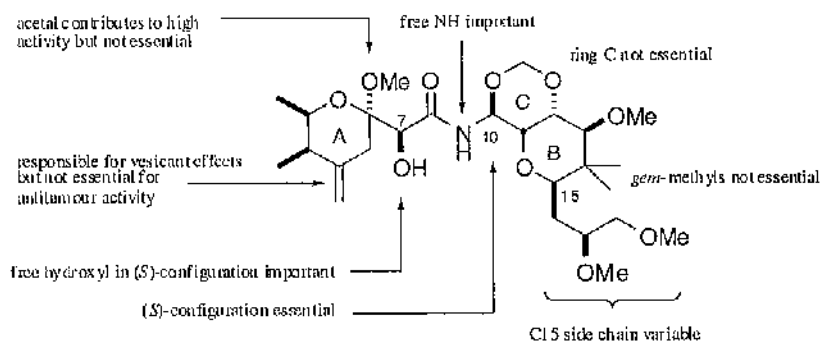


Figure 7.2

7.1.2 RGD peptides as selective vehicle delivery

In 1997, previous work in the Kocienski group⁶¹ had shown that pederin/mycalamide derivatives were extremely potent cytotoxins but insufficiently selective. Therefore, exploitation of the high cytotoxicity of the pederin series would require a means of selective delivery.

7.1.2.1 Integrins as drug targets

Cell-cell and cell-matrix interactions play a major role in biology. An important class of surface receptors are the integrins, which exist in a number of subtypes and are involved in many biological processes, for examples embryonic development, blood coagulation, osteoporosis, cancer, and regulation of the balance between proliferation and death (apoptosis) of a cell. Therefore, selective inhibition of specific integrin subtypes is of great pharmaceutical interest.

The integrins are heterodimeric transmembrane glycoproteins which act as cell surface receptors. They play an important role in signal transduction leading to functional changes in the cell. The integrins consist of an α and a β subunit. Eight separate β and fourteen α subunits are known.¹¹⁵ The $\alpha_v\beta_3$ integrin is highly expressed in many tumour cells where it binds to extracellular matrix proteins which share a common structural motif: the amino acid sequence arginine-glycine-aspartic acid (RGD). The result of such binding is angiogenesis (formation of new blood vessels) and tumour metastasis. Since tumours require angiogenesis to provide sufficient nutrition for rapidly proliferating cancer cells and provide a pathway for cancer cells to enter the blood circulation (the first step in the metastatic cascade), selective inhibition of the $\alpha_v\beta_3$ integrin is of great pharmaceutical interest for the treatment of cancer.

Specific antagonists for the $\alpha_v\beta_3$ integrin based on the RGD sequence and the NGR (asparagine-glycine-arginine) sequence have been identified by Ruoslahti using *in vivo* selection of phage display libraries.¹¹⁶ Although the affinity of NGR for integrins is about three orders of magnitude less than that of RGD peptides, the homing ratio (tumour/control organ) of the phage displaying the NGR motif was three times that of the RGD peptides suggesting the RGD and NGR peptides may bind to different sites on the $\alpha_v\beta_3$ integrin.

7.1.2.2 RGD peptides as integrin antagonists

Kessler and co-workers^{117, 118} screened a library of RGD-based cyclic penta- and hexapeptides containing D-amino acids and discovered highly active and selective $\alpha_v\beta_3$

antagonists with IC₅₀'s in the nanomolar range. Jacobsen and co-workers¹¹⁹ have also described the solid phase synthesis of cyclic RGD peptides with high selectivity (>500,000) for the $\alpha_v\beta_3$ integrin over the $\alpha_{IIb}\beta_3$ integrin involved in platelet aggregation.

The first attempt to harness the high binding affinity of RGD peptides for the selective delivery of a drug to a tumour was reported in 1998 by Ruoslahti and co-workers. They prepared a covalent conjugate of unspecified structure between doxorubicin, a common chemotherapeutic agent with antiangiogenic activity, and the cysteine-rich nonapeptide CDCRGDCFC (RGD-4C). The doxorubicin/RGD-4C conjugate was then used to treat mice bearing tumours derived from human MDA-MB-435 breast carcinoma cells. All of the mice treated with the conjugate outlived the control mice. Histopathological analysis revealed widespread destruction of the tumour architecture whereas tumours of mice treated with doxorubicin alone were minimally affected. Furthermore, the conjugate was less toxic to the liver and heart than free doxorubicin.

7.1.3.1 Aim

The aim of our work is to develop a drug which inhibits tumour angiogenesis and metastasis based on $\alpha_v\beta_3$ integrin antagonists. Our antagonists will consist of a cyclic RGD (or NGR) peptide (the delivery vehicle) to which is attached a potent cytotoxic agent (the warhead) based on the pederin-class of natural products such as **7.1a** (figure 7.3).

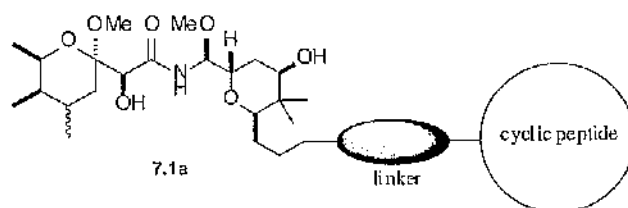


Figure 7.3

7.1.3.2 Choice of analogues

Synthesising conjugates such as **7.1a** required division of the task; whilst Catherine McCusker (PhD student) and Dr Fabrice Anizon (postdoctoral fellow) in the Kocienski group were concentrating their efforts on making cyclic peptides of the Kessler, Ruoslahti or Jacobsen type (**7.1b**, **7.1c** and **7.1d** respectively, figure 7.4), synthesis and biological testing of non-conjugated analogues was performed as described herein.

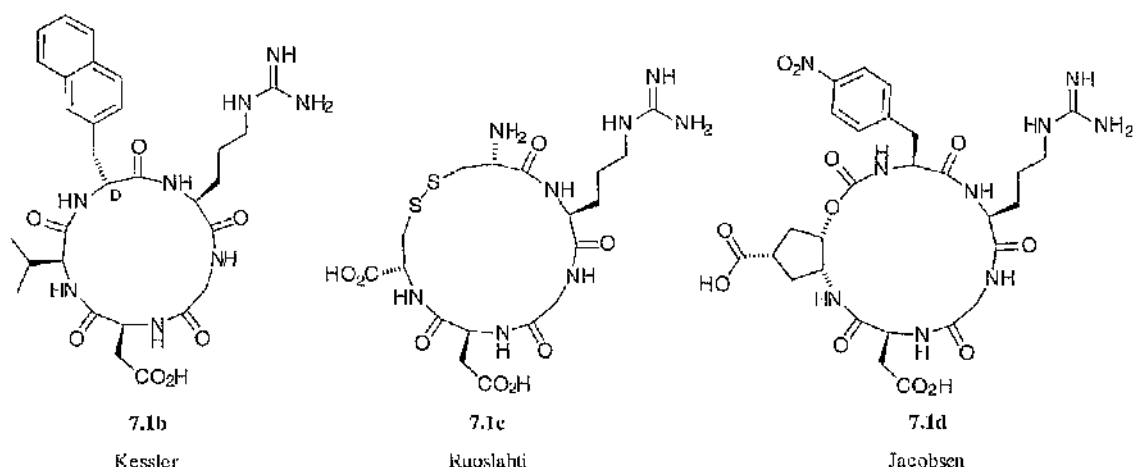


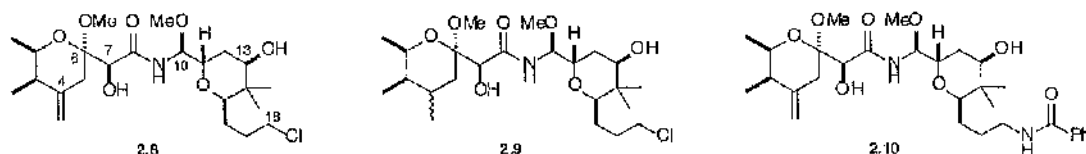
Figure 7.4

Bearing in mind the above mentioned summary of the SAR data of the pederin family the choice of analogues was driven by two factors:

- Firstly, the need to establish that the side chain variants lacking the OMe/OH groups (C17 and C18) were still highly active and could thus be used as a point of attachment
- Secondly, the need to suppress the high acid-lability due to the homoallylic acetal array of the "pederin" part of the conjugates.

It appeared to us that analogues **2.8**, **2.9** and **2.10** could fulfil the above requirements.

7.2 Synthesis of analogues **2.8**, **2.9** and **2.10**

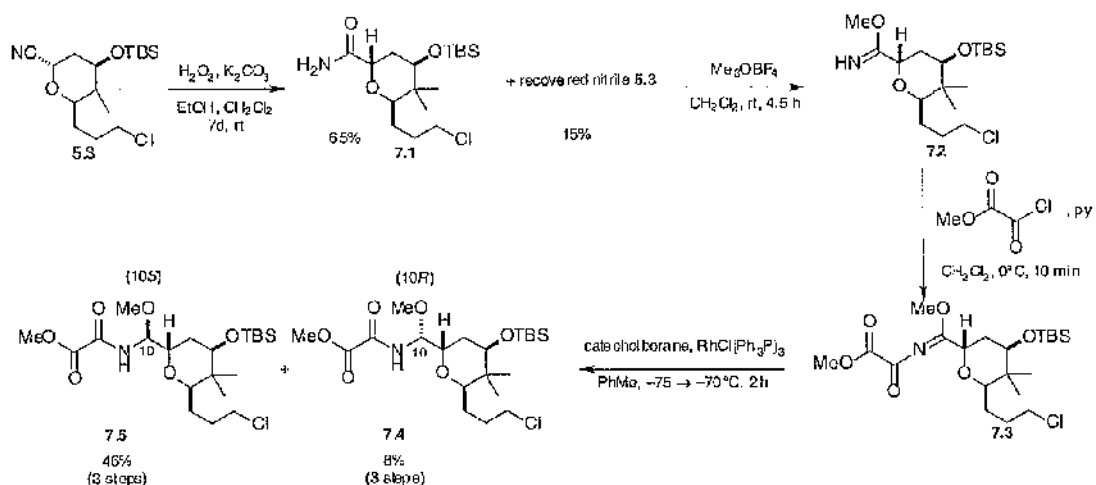


Our syntheses of pederin analogues, uses the readily available nitrile **5.3** as well as the flexibility of the 3-chloropropyl-sidechain approach. The routes are similar to that of pederin (chapter 5) with the exception of the couplings between the left fragment and the right fragment which make use of the tributylstannane **2.3**.

7.2.1 Synthesis of the right fragments of the analogues

Nitrile **5.3** (scheme 7.1) was hydrolysed to give amide **7.1**,^{120, 121} which was converted to the chlorinated right fragment **7.5** in 3 steps including a rhodium-mediated reduction of the *N*-acylimidate **7.3** giving a diastereomeric mixture of **7.5** and **7.4** (10*S*:10*R* = 5.5:1). The diastereomeric ratio was determined by ¹H NMR (400 MHz, CDCl₃) spectroscopy by

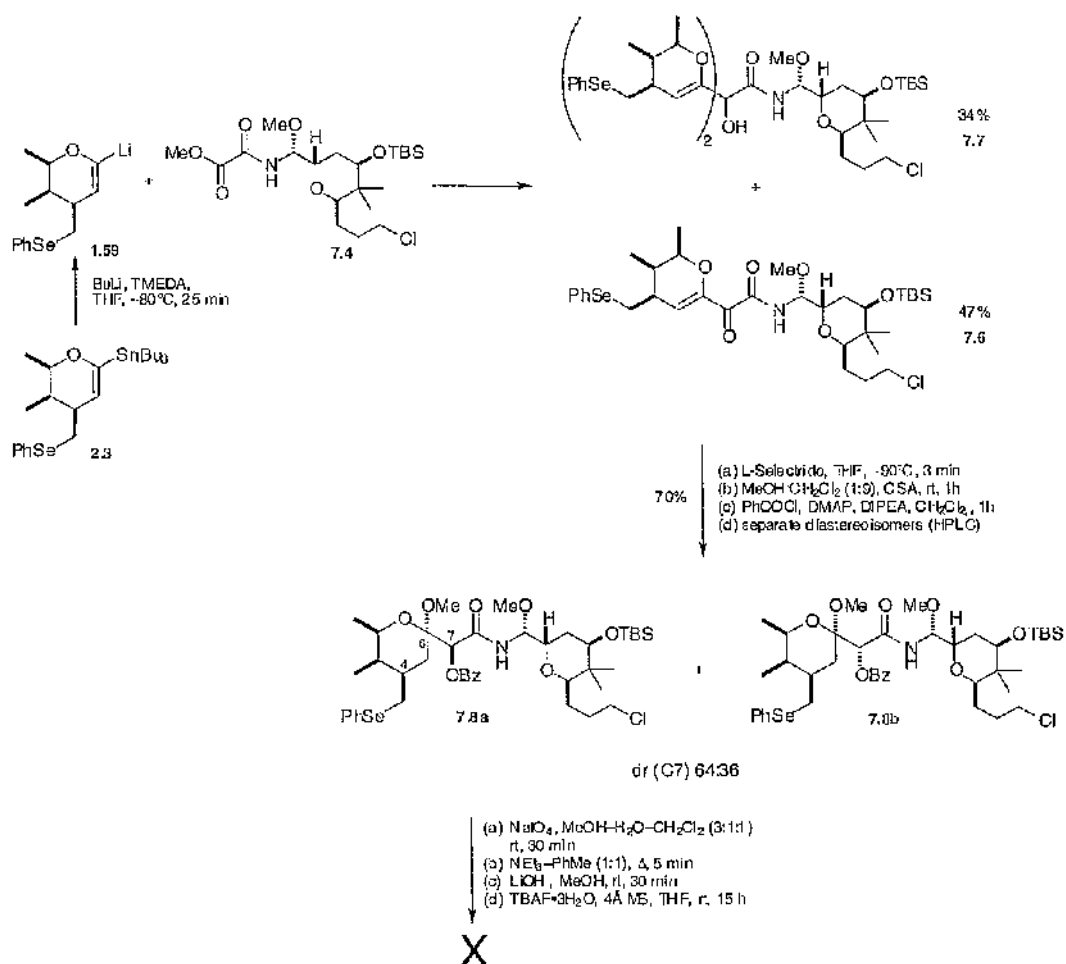
integration of signals deriving from C10-H at $\delta = 5.21$ ppm (dd, J 9.8, 6.7, major) and 5.10 ppm (dd, J 9.9, 3.4, minor). Separation and purification of **7.4** and **7.5** was easily achieved by column chromatography.



Scheme 7.1

7.2.2 Synthesis of analogue 2.8 with 10(R) stereochemistry

Previous experience had shown that the best yields in the coupling reaction of the two halves were achieved when 2.5–4 equivalents of the trimethylstannane **2.2** were transmetalated with BuLi prior to reaction with N -acylimidate. When the same protocol with tributylstannane **2.3** was used to create the bridge in **7.8**, a minor byproduct **7.7** (37%) was isolated suggesting that the transmetalation step is more efficient with the tributylstannane **2.3** than the trimethylstannane **2.2**.

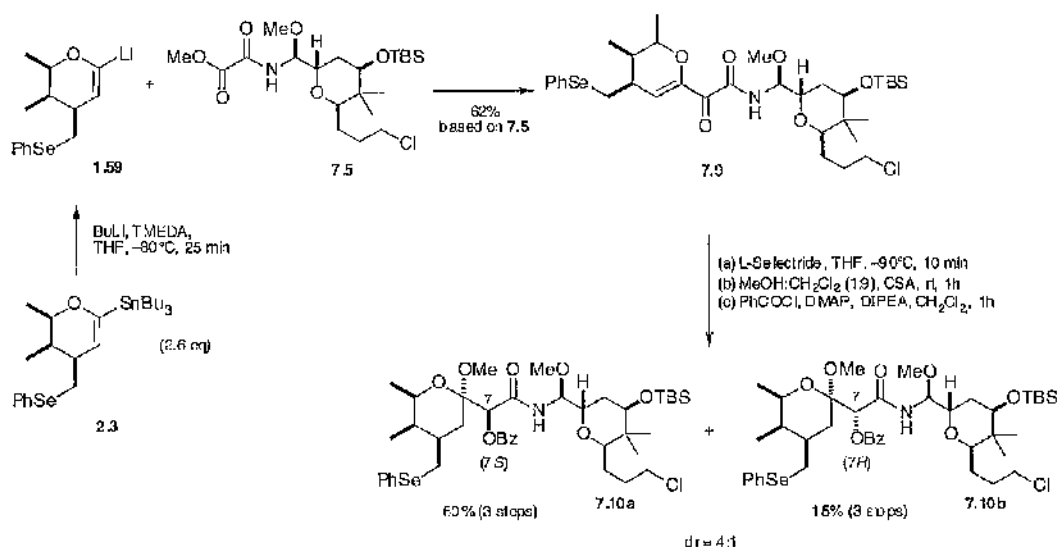


Scheme 7.2

Benzoates **7.8a,b** were obtained following the previously described 3-step sequence and were separated by HPLC. The diastereomeric ratio of the reduction step using *L*-Selectride step (**7.8a**:**7.8b** = 64:36) was determined by ^1H NMR (400 MHz, CDCl_3) spectroscopy by integration of signals (s) of C7-H at $\delta = 5.46$ ppm (major) and 5.73 ppm (minor). NOE experiments (400 MHz, CDCl_3) were not conclusive in the determination of the stereochemistry of each benzoate **7.8a** and **7.8b**, and although compound **7.8b** is crystalline, its state of crystallisation ("soft" crystals in a "feather" manner) did not allow us to obtain X-Ray diffraction data. Comparison of the chemical shifts of C7-H in ^1H NMR (400 MHz, CDCl_3) spectroscopy and C7 in ^{13}C NMR (400 MHz, CDCl_3) spectroscopy with the benzoates in the pederin, mycalamides and pederin analogues series led us to the tentative conclusion that the stereochemistry of the major product (**7.8a**) was (7*S*) (scheme 7.2). Unfortunately, after oxidative cleavage of phenyl selanylether, and deprotection of the benzoate, the TBAF deprotection step was more difficult than expected and yielded a complex mixture of products.

7.2.3 Coupling of tributylstannane 2.3 with 7.5 and synthesis of analogues 2.8, 2.9, 2.10.

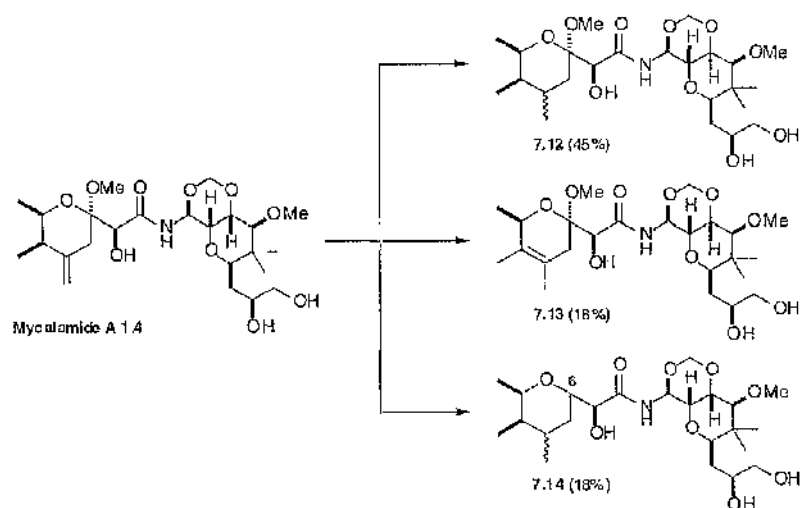
Synthesis of several analogues with the natural stereochemistry at the C10 centre were synthesised as described in schemes 7.3 and 7.5. It is noteworthy that the coupling reaction gave adduct **7.9** in good yield (62%) when 2.6 equivalents of tributylstannane **2.3** was used. Benzoates **7.10ab** were obtained with a 4:1 diastereoselectivity at the C7-centre (Scheme 7.3). The diastereoselectivity was determined by ^1H NMR (400 MHz, CDCl_3) spectroscopy by integration of signals (dd) of C10-H at $\delta = 5.26$ ppm (**7.10a**) and 5.73 ppm (**7.10b**).



Scheme 7.3

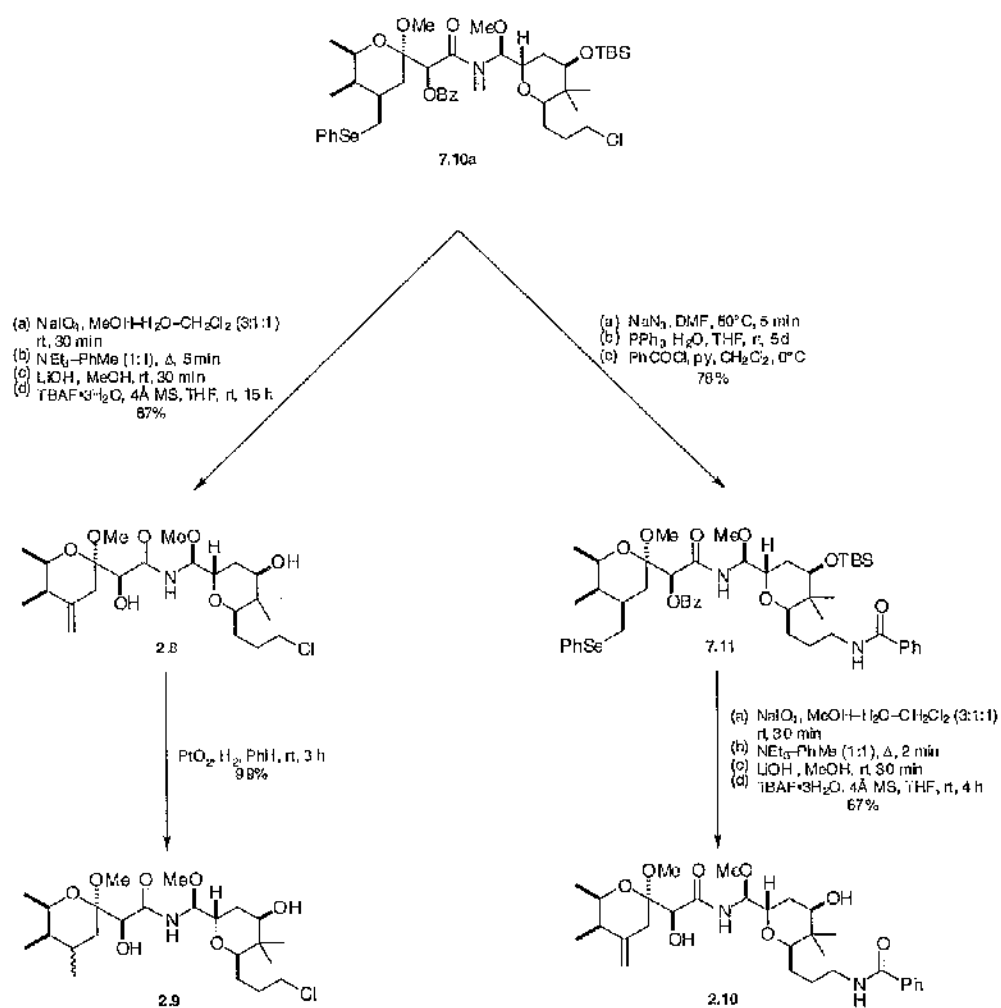
Synthesis of pederin analogue **2.8** with a chloropropyl sidechain followed the typical procedures already described (scheme 7.5). Hydrogenation of the exocyclic double bond was more problematic. Indeed, Munro, had already attempted to obtain dihydromycalamide A **7.12** by catalytic hydrogenation.⁷¹ He showed that if the reaction was carried out using Palladium-on-charcoal in methanol, the two diastereomers of dihydromycalamide A (α,β) **7.12** were obtained in 45% yield, as well as two new products (scheme 7.4). The first one (**7.13**, 18%) is the result of the transposition of the exocyclic double bond into the ring to form tetrasubstituted double bond whereas the second one (**7.14**, 18%) had the 6-methoxy replaced by a proton. Munro also described the reaction carried out with Adam's catalyst ($\text{PtO}_2 \cdot x\text{H}_2\text{O}$) in methanol yielding, this time, mainly the desired products. Studies on the effect of solvent in hydrogenation reactions have shown that benzene is effective as an isomerisation inhibitor whether or not it is used on its own or mixed with other solvents.¹²² Since our first attempt at homogeneous catalysed hydrogenation using Wilkinson's catalyst $[(\text{PPh}_3)\text{RhCl}]$ on 1.0 mg scale of **2.8** was not successful, the reaction was carried out using Adams' platinum oxide catalyst in benzene

to yield the two diastereoisomers **2.9** as an inseparable mixture (dr = 7:3). The diastereometric ratio was determined by integration of the signal derived from C7-H (1H, s) at δ = 3.96 ppm (major) and 4.02 ppm (minor).



Scheme 7.4

To synthesise the benzamide analogue **2.10**, the chlorine of the side chain was displaced by refluxing **7.10a** in the presence of sodium azide in dimethyl formamide to yield the azidopropyl side chain. Reduction of the azide was then performed under mild condition using triphenylphosphine and water following a procedure described by Vaultier¹²³ to yield the corresponding amine derivative which was then acylated with benzoyl chloride in the presence of pyridine to give the desired benzamide **7.11** in good yield (78% over 3 steps). Obtaining the benzamide analogue **2.10** was achieved by using the same last four steps as previously described.



Scheme 7.5

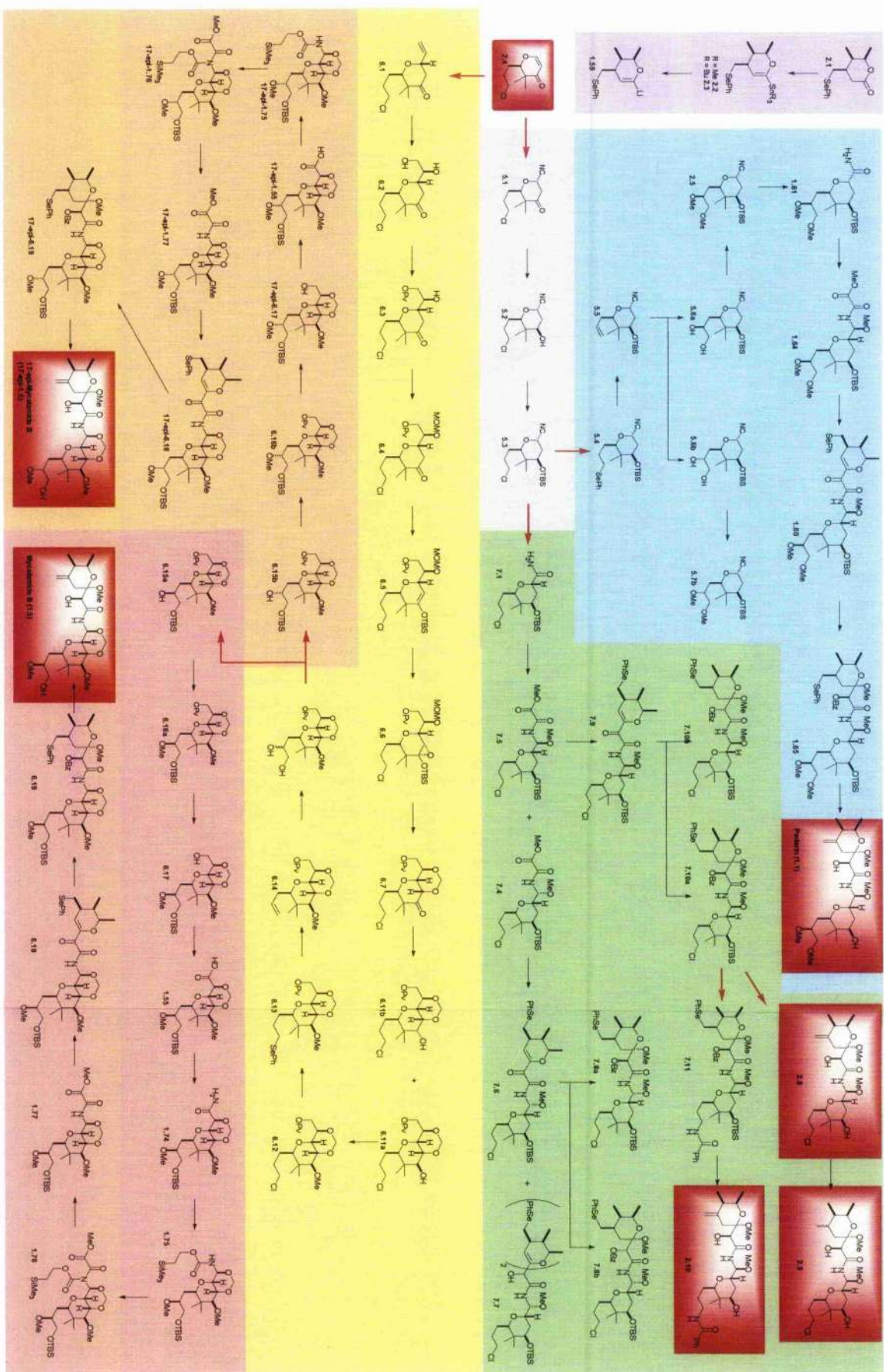
Chapter 8 : Biological activity

Samples have been submitted for biological testing at AstraZeneca (Macclesfield) and we are awaiting results.

Chapter 9 : Summary

The aim of the study was to develop a highly efficient, flexible and economical route towards the synthesis of pederin family members. By completing the total synthesis of pederin **1.1**, mycalamide B **1.5**, 17-epi-mycalamide B **17-epi-1.5**, and some analogues of pederin (**2.8**, **2.9** and **2.10**) we have shown that both lactone **2.1** and enone **2.4** with its 3-chloropropyl side chain were judiciously chosen intermediates which fulfilled our objectives. Although the construction of the C17 centre in both the synthesis of pederin **1.1** and mycalamide B **1.5** occurred with little stereocontrol, every other challenging problems has been addressed. Indeed, the C13 centre was obtained with good to high stereocontrol using a reduction under Luche conditions for the pederin-like compounds and under Meerwein-Pondorf-Verley conditions in the mycalamide series. The construction of the *cis*-2,4,7-trioxabicyclo[4.4.0]decalin ring was performed by a high yielding ring closure procedure using P₂O₅/dimethoxymethane which occurred with high stereocontrol. The remaining elaboration of the difficult *N*-aminal bridge with its C10 centre found solution in the well precendented Rh-catalysed reduction of an *N*-acylimidate for the pederin-like compounds whereas Curtius and Hofmann rearrangements were used efficiently in the mycalamide series. Finally, the metallated dihydropyran approach to link the two fragments, which had been set as a requirement of every synthesis, has been improved by using the tributylstannane **2.3**. An unprecedented and unpublished methodology using Lipshutz's mixed trialkylstannyl cyano cuprates was applied in the synthesis of **2.3**.

A summary of the syntheses presented herein is shown in scheme 9.1.



Scheme 9.1

Chapter 10. Experimental

10.1 General Experimental Details

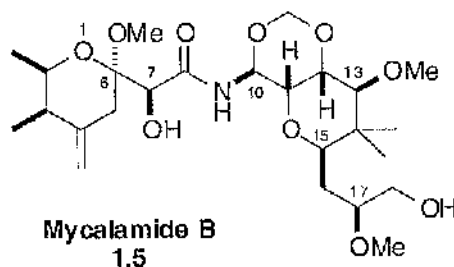
Reactions requiring anhydrous conditions were conducted in flame-dried apparatus under a static atmosphere of dry argon or nitrogen. Organic extracts were evaporated at 5-20 mm Hg using a Buchi rotary evaporator. Where appropriate, solvents and reagents were dried by standard methods,¹²⁴ i.e. by distillation from the usual drying agent prior to use; diethyl ether and tetrahydrofuran were distilled from Na/benzophenone and used fresh. Acetonitrile, pentane, pyridine, dimethylsulfoxide, dichloromethane, *N,N*-dimethylformamide, toluene diisopropylethylamine and triethylamine were distilled from CaH₂ and stored over 4 Å molecular sieves under nitrogen or KOH. Methanol was distilled from the corresponding magnesium methoxide. Hexanes (bp 40-60°C) for chromatography was distilled before use. Iodine and catechol were sublimed at 0.5 mm Hg and stored under nitrogen. For best results, copper (I) iodide was extracted with THF in a Soxhlet apparatus and stored in the dark. The Dess-Martin periodinane reagent^{125, 126} was prepared according to the literature and stored at -20°C under nitrogen. Commercial organometallics were used as supplied and alkylolithium reagents were titrated against 1,3-diphenylacetone *p*-tosylhydrazone.¹²⁷

All reactions were magnetically stirred and were monitored by Thin Layer Chromatography (TLC) using Macherey-Nagel Alugram Sil G/UV₂₅₄ pre-coated aluminium foil sheets, layer thickness 0.25 mm. Compounds were visualised by UV (254 nm), 20 wt% phosphomolybdic acid (PMA) in ethanol, anisaldehyde, vanillin followed by H₂SO₄, potassium permanganate with heating or Ceric sulphate. Flash chromatography was performed on Fisher Scientific Matrex Silica 60 (35-70 micron, code No. S/0683/70).¹²⁸ Preparative TLC were performed on Macherey-Nagel SIL 9-200 UV₂₅₄ pre-coated glass sheets (20 x 20 cm, layer thickness 2 mm).

Optical rotations were recorded on an Optical Activity AA-100 polarimeter. Melting points were measured on a Griffin electrothermal apparatus and are uncorrected. IR spectra were recorded on a Perkin Elmer 1600 series FTIR spectrometer as thin films supported on sodium chloride plates. Absorptions are reported as values in cm⁻¹ and weak absorptions are not reported.

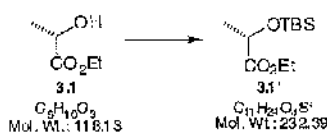
¹H and ¹³C NMR spectra were recorded in Fourier Transform mode at the field strength specified. All spectra were obtained in CDCl₃ or C₆D₆ solution in 5 mm diameter tubes, and the chemical shift in p.p.m. is quoted relative to the residual signals of chloroform (δ_H 7.27, δ_C 77.0) or C₆H₆ (δ_H 7.10, δ_C 126.7) as the internal standard unless otherwise specified. Multiplicities in the ¹H NMR spectra are described as: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, and app = apparent. Coupling constants (*J*) are reported in Hz. Numbers in parenthesis following the chemical shift in the ¹³C NMR spectra refer to the number of protons attached to that carbon as revealed by the Distortionless Enhancement by Phase Transfer (DEPT) spectral editing technique, with secondary pulses at 90° and 135°. Signal assignments were based on COSY, HMQC and HMBC correlations. Mycalkunide numbering was used throughout in assigning NMR signals. Low and high resolution mass spectra were run on a JEOL MStation JMS-700 spectrometer. Ion mass/charge (*m/z*) ratios are reported as values in atomic mass units followed, in parenthesis, by the peak intensity relative to the base peak (100%). Mass spectra were recorded on samples judged to be ≥95% pure by ¹H and ¹³C NMR spectroscopy unless otherwise stated.

Numbering of all intermediates uses the mycalamide system as shown below:



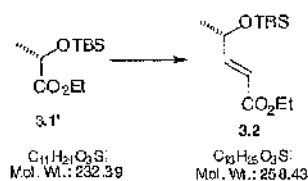
10.2 Synthesis of lactone 2.1

Ethyl (*S*)-*O*-(*tert*-butyldimethylsilyl)lactate (3.1')



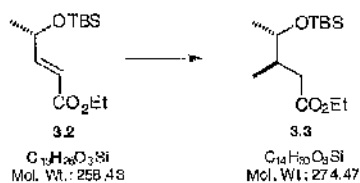
The title compound prepared in 99% yield (0.54 mol scale) from ethyl (*S*)-lactate by the procedure of Smith, Kocienski and Street gave $[\alpha]_D^{22} -30.0$ (c 2.5, CHCl_3); lit. $[\alpha]_D -30.5$ (c 2.1, CHCl_3).¹²⁹

Ethyl (*S*)-4-(*tert*-butyldimethylsilyloxy)pent-2-enoate (3.2)



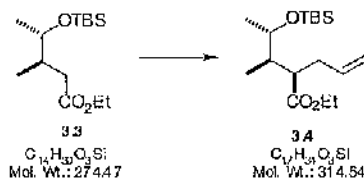
The title enoate ester 3.2 was prepared in 72% yield (0.175 mol scale) by the method of Annunziata et al.⁷⁸

Ethyl (3*R*,4*S*)-4-(*tert*-butyldimethylsilyloxy)-3-methylpentanoate (3.3)



The title ester 3.3 was prepared in 75% yield (71 mmol scale) by the method of Yamamoto et al.⁸⁰

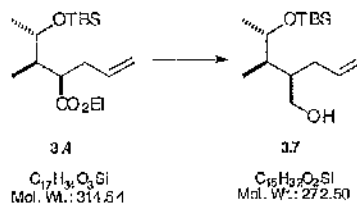
Ethyl (2*R*,3*R*,4*S*)-2-allyl-4-(*tert*-butyldimethylsilyloxy)-3-methylpentanoate (3.4)



Ester **3.3** (24.0 g, 91.6 mmol) was added dropwise *via* syringe to a stirred solution of potassium bis(trimethylsilyl)amide (23.3 g, 80%, 93.0 mmol) in THF (350 ml) at $-78\text{ }^{\circ}\text{C}$. The reaction mixture was stirred at $-78\text{ }^{\circ}\text{C}$ for 30 min and then allyl bromide (40 ml, 456 mmol) was added dropwise. The reaction mixture was stirred at $-78\text{ }^{\circ}\text{C}$ for 3 h, quenched with saturated aqueous NH_4Cl and extracted with hexanes (2 x 100 ml). The combined organic extracts were washed with brine (100 ml), dried (Na_2SO_4) and concentrated. The residue was purified by short path distillation to give ester **3.4** (22.2 g, 73.4 mmol, 80%) as a colourless oil; bp $84\text{--}88\text{ }^{\circ}\text{C}$ at 0.5 mm Hg as a 22:1 mixture of diastereoisomers according to integration of the doublets at δ 0.06 (minor) and 0.04 (major) as revealed in the ^1H NMR spectrum (CDCl_3).

Spectroscopic data (^1H NMR, ^{13}C NMR, IR, and $[\alpha]_D$) in agreement with Dr C. Smith data.⁷⁷

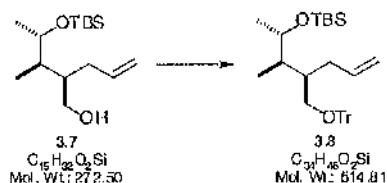
(2*R*,3*R*,4*S*)-2-Allyl-4-*O*-(*tert*-butyldimethylsilyl)-3-methyl-1,4-pentandiol (3.7)



A solution of DIBAL-H (neat, 28 ml, 156 mmol) was added dropwise to a stirred solution of ester **3.4** (21.0 g, 66.9 mmol) in CH_2Cl_2 (30 ml) between $5\text{--}10\text{ }^{\circ}\text{C}$ over 40 min. The reaction mixture was stirred at $-5\text{ }^{\circ}\text{C}$ for 1 h. A mixture of water (4 ml) and acetone (40 ml) was added dropwise over 45 min, keeping the temperature of the reaction mixture below $20\text{ }^{\circ}\text{C}$. The clear solution became a white solid. Aqueous HCl (2M, 230 ml) was then added over 15 min. The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 100 ml). The combined extracts were dried (MgSO_4) and concentrated. Kugelrohr distillation afforded alcohol **3.7** (16.2 g, 59.6 mmol, 89%) as a colourless oil; bp $140\text{--}145\text{ }^{\circ}\text{C}$ (bath) at 0.02 mm Hg.

Spectroscopic data (^1H NMR, ^{13}C NMR, IR, and $[\alpha]_D$) in agreement with Dr C. Smith data.⁷⁷

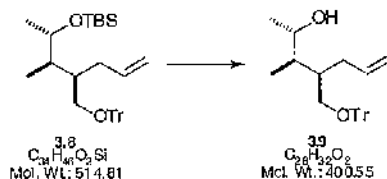
(2R,3R,4S)-2-Allyl-4-O-(*tert*-butyldimethylsilyl)-3-methyl-1-O-triphenylmethyl-1,4-pentanediol (3.8)



A solution of alcohol **3.7** (15.0 g, 55.0 mmol), trityl chloride (17.3 g, 62.0 mmol), triethylamine (22 ml, 157 mmol) and DMAP (610 mg, 5.0 mmol) in CH_2Cl_2 (50 ml) was stirred at rt for 12 h, poured onto aqueous saturated $NaHCO_3$ and extracted with CH_2Cl_2 (3 x 100 ml) and concentrated. The oily residue was dissolved in Et_2O (100 ml) treated with hexanes (200 ml) and washed with water (500 ml). The organic layer was dried (Na_2SO_4) and concentrated. The residue was filtered through a pad of silica gel (5% Et_2O in hexanes) to give trityl ether **3.8** (26.6 g, 51.7 mmol, 94%) as a colourless oil

Spectroscopic data (1H NMR, ^{13}C NMR, IR, and $[\alpha]_D$) in agreement with Dr C. Smith data.⁷⁷

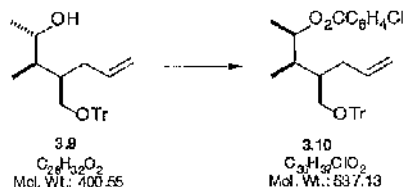
(2R,3R,4S)-2-Allyl-3-methyl-1-O-triphenylmethyl-1,4-pentanediol (3.9)



A solution of TBS ether **3.8** (53.6 g, 104.0 mmol) and TBAF trihydrate (53.0 g, 168.0 mmol) in THF (200 ml) was stirred at reflux for 5 h. After cooling to rt, the mixture was poured onto water (1 l) and extracted with Et_2O (3 x 150 ml). The combined organic extracts were dried (Na_2SO_4) and concentrated to give crude alcohol **3.9** (40.4 g, 100.9 mmol, 97%) as a colourless oil which was immediately used in the next step. Data was obtained by purification of a small sample by column chromatography (SiO_2 , 5–10% Et_2O in hexanes).

Spectroscopic data (1H NMR, ^{13}C NMR, IR, and $[\alpha]_D$) in agreement with Dr C. Smith data.⁷⁷

(2R,3R,4R)-2-Allyl-4-O-(4-chlorobenzoyl)-3-methyl-1-O-triphenylmethyl-1,4-pentanediol (3.10)

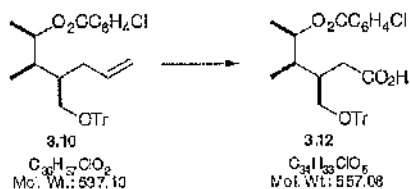


A solution of diisopropyl azodicarboxylate (16.05 ml, 81.5 mmol) in THF (10 ml) was added dropwise to a stirred solution of alcohol **3.9** (18.5 g, 46.3 mmol), triphenylphosphine (21.4 g, 81.6 mmol) and *p*-chlorobenzoic acid (12.8 g, 81.7 mmol) in THF (150 ml). The temperature of the reaction mixture was maintained between $-10\text{ }^{\circ}C$ and $0\text{ }^{\circ}C$. The reaction mixture was stirred for 3 h between $-10\text{ }^{\circ}C$ and $0\text{ }^{\circ}C$. Water (1 ml) was added and the mixture was stirred at rt for 15 min before concentration. The residual oil was dissolved in Et_2O (50 ml) and hexanes (100 ml) were added dropwise to cause formation of white

crystals. The crystals (triphenylphosphine oxide) were filtered off and washed with hexanes (3 x 50 ml). The filtrate was extracted with 2M aqueous NaOH (2 x 30 ml), water (50 ml) and brine (50 ml), dried (Na₂SO₄) and concentrated *in vacuo*. The residue was purified by column chromatography (SiO₂ 0-4% Et₂O in hexanes) to give the *p*-chlorobenzoate **3.10** as a colourless oil that crystallised on standing (19 g, 35 mmol, 76%) and its C3 epimer (0.6 g, 1.1 mmol, 2.4%).

Spectroscopic data (¹H NMR, ¹³C NMR, IR, and [α]_D) in agreement with Dr C. Smith data.⁷⁷

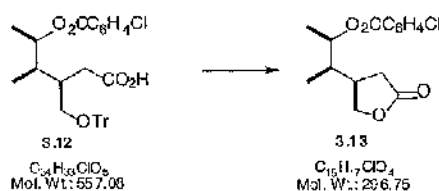
(3*R*,4*R*,5*R*)-5-(4-Chlorobenzoyloxy)-4-methyl-3-(triphenylmethoxymethyl) hexanoic acid (3.12)



Oxidative cleavage of the olefin was accomplished by the procedure of Sharpless et al.¹¹¹ NaIO₄ (18.3 g, 85.7 mmol) was added to a stirred mixture of olefin **3.10** (11.0 g, 20.4 mmol), CCl₄ (41 ml), acetonitrile (41 ml) and water (62 ml). After 15 min RuCl₃·3H₂O (270 mg, 1.0 mmol) was added and the reaction mixture stirred vigorously for 7 h. The mixture was poured onto water (600 ml), the organic layer removed and the aqueous phase extracted with CH₂Cl₂ (3 x 150 ml). The combined organic extracts were dried (MgSO₄) and concentrated *in vacuo*. The residue was purified by column chromatography (SiO₂ 200 g, 5% EtOAc in hexanes) to give acid **3.12** (10.8 g, 19.4 mmol, 95%) as a stable white foam, mp 55–57 °C;

Spectroscopic data (¹H NMR, ¹³C NMR, IR, and [α]_D) in agreement with Dr C. Smith data.⁷⁷

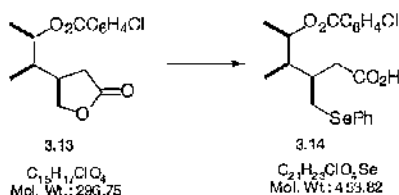
(*R*)-4-[(1*R*,2*R*)-2-(4-Chlorobenzoyloxy)-1-methylpropyl]-dihydrofuran-2(3*H*)-one (3.13)



A solution of acid **3.12** (10.8 g, 19.3 mmol) and *p*-toluenesulfonic acid (490 mg, 2.6 mmol) in MeOH (180 ml) was stirred at rt for 4 h before concentration *in vacuo*. The residue was purified by column chromatography (SiO₂ 120 g, 10-50% Et₂O in hexanes) to give lactone **3.13** (4.0 g, 13.5 mmol, 71%) as a white solid. The lactone **3.13** was further purified by recrystallisation from hexanes–Et₂O to remove the minor diastereoisomers; mp 69.5–70 °C (hexanes–Et₂O).

Spectroscopic data (¹H NMR, ¹³C NMR, IR, and [α]_D) in agreement with Dr C. Smith data.⁷⁷

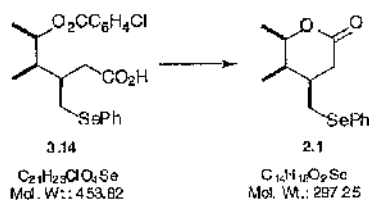
(3*R*,4*R*,5*R*)-5-(4-Chlorobenzoyloxy)-4-methyl-3-(phenylselenenylmethyl) hexanoic acid (3.14)



The lactone cleavage was accomplished using sodium phenyl selenide as described in the literature.⁸⁵ Sodium borohydride (350 mg, 9.25 mmol) was added portionwise to a stirred yellow suspension of diphenyl diselenide (1.6 g, 5.15 mmol) in EtOH (5.8 ml) causing exothermic reaction and gas evolution. Lactone **3.13** (1.0 g, 3.37 mmol) was added to the colourless solution of sodium phenyl selenide. The resulting mixture was stirred at reflux for 10 h. After cooling to rt, the reaction mixture was diluted with Et₂O (8 ml) and treated with aqueous HCl (2M, 5 ml). The layers were separated, and the aqueous phase was extracted with Et₂O (3 x 20 ml). The combined organic extracts were washed with aqueous NaHCO₃ (2 x 10 ml), dried (MgSO₄) and concentrated *in vacuo*. The residue was purified by column chromatography (SiO₂ 20 g, 10-40% Et₂O in hexanes) to give acid **3.14** as a yellow oil (1.05 g, 2.72 mmol, 80%).

Spectroscopic data (¹H NMR, ¹³C NMR, IR, and [α]_D) in agreement with Dr C. Smith data.⁷⁷

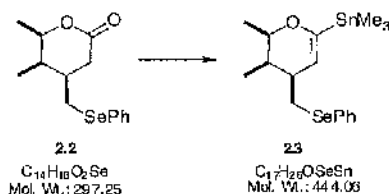
(2*R*,3*R*,4*R*)-Tetrahydro-5,6-dimethyl-4-phenylselenenylmethyl-2*H*-pyran-2-one (2.1)



Reductive cleavage of the *p*-chlorobenzoate ester was accomplished according to the procedure of Trost et al.⁸⁶ ¹³⁰BuLi (3.75 ml, 2.32 M in hexanes, 8.7 mmol) was added dropwise to a solution of DIBAL-H (neat, 8.7 mmol, 1.55 ml) in CH₂Cl₂ (16 ml) at -5 °C. THF (32 ml) was then added, the mixture was cooled to -78 °C and a solution of the ester **3.14** (1.31 g, 2.9 mmol) in THF (32 ml) was added *via* cannula. The mixture was allowed to warm to -20 °C over 5 min. and stirred at -20 °C for 3 h. The mixture was then treated with aqueous HCl (2M, 35 ml, 70 mmol), and Et₂O (30 ml) and stirred vigorously for 24 h. The organic layer was removed and the aqueous phase extracted with Et₂O (2 x 40 ml). The combined organic extracts were dried (MgSO₄) and concentrated *in vacuo*. The residue was purified by column chromatography (SiO₂ 40 g, 10-30% Et₂O in hexanes) to give **2.1** as a clear colourless oil (619 mg, 2.08 mmol, 72%).

¹H NMR and ¹³C NMR spectroscopic data agree with the literature.³²

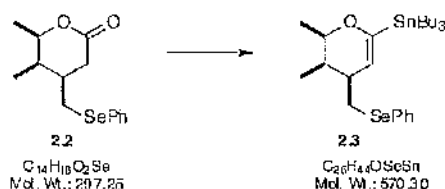
(2*R*,3*R*,4*S*)-3,4-Dihydro-2,3-dimethyl-4-phenylselenylmethyl-6-trimethylstannyl-2*H*-pyran (2.2)



The conversion of lactone 2.1 (150 mg, 0.50 mmol) to 2.2 (156 mg, 0.35 mmol) was accomplished in 70% yield according to a reported procedure.³²

Tributyl-[(4*S*,5*R*,6*R*)-5,6-dimethyl-4-phenylselenylmethyl-5,6-dihydro-4*H*-pyran-2-yl]-stannane (2.3)

• From lactone 2.1



Procedure A^{32, 75}

To the lactone 2.1 (944 mg, 3.16 mmol) in THF (8 ml) at $-78^{\circ}C$ was added HMPA (0.72 ml, 4.12 mmol) followed by LiHMDS (4.6 ml, 4.12 mmol, 0.9 M in THF). After 2 h at $-78^{\circ}C$, $PhNTf_2$ (1.44 g, 4.12 mmol) was added as a solid to the reaction mixture which was then allowed to warm gradually to $0^{\circ}C$. After 2 h at $0^{\circ}C$ hexabutyltin (1.5 ml, 3.00 mmol) followed by $Pd(PPh_3)_4$ (109 mg, 0.095 mmol) and then lithium chloride (805 mg, 19.0 mmol) were added. The pale yellow/brown solution was refluxed for 14 h and the resulting black solution was poured onto saturated aqueous $NaHCO_3$ (10 ml) and extracted with a 1:1 solution of hexanes: Et_2O (3 x 10 ml). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (deactivated Al_2O_3 (5% H_2O), 1% Et_3N in hexanes) gave 252 mg (0.44 mmol, 14%) of stannane 2.3 as a colourless oil.

Procedure B^{89, 131}

To a solution of KHMDS (4.45 ml, 2.22 mmol, 0.5 M in PhMe) in THF (4.5 ml) at $-78^{\circ}C$ was slowly added a solution of lactone 2.1 (508 mg, 1.71 mmol), $PhNTf_2$ (672 mg, 1.88 mmol) in THF (4.5 ml) over 25 min to form the intermediate enoltriflate 3.21. The formation of enoltriflate was followed by TLC.

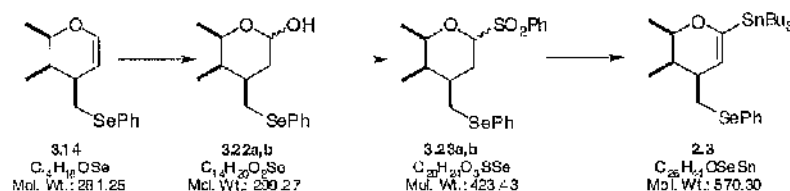
Meanwhile, to a suspension of CuCN (200 mg, 2.22 mmol) in THF (5.6 ml) at $-78^{\circ}C$, was added dropwise $nBuLi$ (1.95 ml, 4.44 mmol, 2.27 M in hexane). The cooling bath was temporarily removed (2 min) and the clear pale yellow solution was then cooled again at $-78^{\circ}C$. After 5 min at $-78^{\circ}C$, Bu_3SnH (1.2 ml, 4.44 mmol) was added dropwise (H_2 evolution) and the dark yellow solution was then stirred at $-78^{\circ}C$ for another 20 min.

The enoltriflate solution was then quickly transferred using a large cannula to the copper complex solution and the reaction mixture was then stirred at $-78^{\circ}C$ for 5 min before being poured onto a 100 ml solution

containing 10 ml of concentrated aqueous NH_3 and 90 ml of saturated aqueous NH_4Cl . After dilution with CH_2Cl_2 (10 ml) and strong shaking (5 min), the phases were separated and the blue aqueous layer was extracted with CH_2Cl_2 (3 x 30 ml). The combined extracts were dried (Na_2SO_4) and concentrated *in vacuo*. ^1H NMR (400MHz, CDCl_3) spectroscopy showed a 86.4:13.5 ratio of desired stannane **2.3** : dihydropyran **3.14** byproduct.

Purification by column chromatography (deactivated Al_2O_3 (5% H_2O), 500 g, column diameter = 8 cm, 1% Et_3N in hexanes) gave 837 mg (1.46 mmol, 85%) of stannane **2.3** as a colourless oil: $[\alpha]_{\text{D}}^{18} -7.4$ (c 1.1, CHCl_3); ν_{max} film/ cm^{-1} 2955, 2926, 2870, 2853, 1596, 1579, 1476, 1462, 1437, 1080, 734, 690; δ_{H} (400 MHz, CDCl_3): 7.43-7.35 (2H, m, Harom), 7.20-7.13 (3H, m, Harom), 4.35 (1H, tt, $J_{\text{H-H}}$ 1.7, $J_{\text{H-Sn}}$ 14.4, C5-H), 3.84 (1H, dq, J 6.5, 1.4, C2-H), 2.75 (2H, d, J 8.2, $\text{CH}_2\text{-Se}$), 2.67-2.60 (1H, m, C4-H), 1.80-1.72 (1H, m, C3-H), 1.50-1.60 (6H, m, $\text{Sn-}[\text{CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_3]_3$), 1.29-1.16 (6H, m (6 lines), $\text{Sn-}[\text{CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_3]_3$), 1.08 (3H, d, J 6.5, C2-Me), 0.82 (6H, t, J 8.0, $\text{Sn-}[\text{CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_3]_3$), 0.81 (9H, t, J 7.3, $\text{Sn-}[\text{CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_3]_3$), 0.69 (3H, d, J 6.8, C3-Me); δ_{C} (100 MHz, CDCl_3) 162.6 (0, C6), 132.6 (1, 2C, Carom), 130.5 (0, Carom), 129.0 (1, 2C, Carom), 126.7 (1, Carom), 112.5 (1, t, $J_{\text{C-Sn}}$ 30, C5), 75.3 (1, t, $J_{\text{C-Sn}}$ 10, C2), 38.4 (1, t, $J_{\text{C-Sn}}$ 16, C4), 33.9 (1, C3), 31.6 (2, $\text{CH}_2\text{-Se}$), 29.0 (2, 3C, t, $J_{\text{C-Sn}}$ 10, $\text{Sn-}[\text{CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_3]_3$), 27.1 (2, 3C, $J_{\text{C-Sn}}$ 26, $\text{Sn-}[\text{CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_3]_3$), 18.5 (3, C2-Me), 13.7 (3, 3C, $\text{Sn-}[\text{CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_3]_3$), 9.6 (2, 3C, tt, $J_{\text{C-Sn}}$ 170, 163, $\text{Sn-}[\text{CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_3]_3$), 5.3 (3, C3-Me). m/z (EI) 573 (92), 571 $[(\text{M}+\text{H})^+]$, 100%, 569 (76), 415 (25), 413 (18), 308 (7), 283 (20), 281 (10); Found : (EI), 570.1587. $\text{C}_{26}\text{H}_{44}\text{OSeSn}$ requires M , 570.1587.

• From dihydropyran **3.14**



Synthesis of stannane **2.3** from **3.14** followed a S. Ley procedure.⁹⁰

dihydropyran **3.14** to lactols **3.22a,b**

To a solution of dihydropyran **3.14** (300 mg, 1.06 mmol) in THF (1 ml) was added 2N HCl (1 ml) and the reaction was stirred at room temperature. After 10 h, the reaction mixture was diluted with CH_2Cl_2 (10 ml) and then poured slowly onto ice-cooled saturated aqueous NaHCO_3 (10 ml). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 10 ml). The combined organic extracts were dried (MgSO_4) and concentrated *in vacuo* to give a mixture of inseparable lactols **3.22a,b** (310 mg, 1.0 mmol, 98%) which was used directly in the next step. The diastereomeric ratio (dr = **3.22a**:**3.22b** = 56:44) was determined by ^1H NMR (400 MHz, CDCl_3) spectroscopy by integration of signals (d or dd) of C6-H at δ = 5.20 ppm (minor, OH in axial position) and 4.61 ppm (minor, OH in equatorial position).

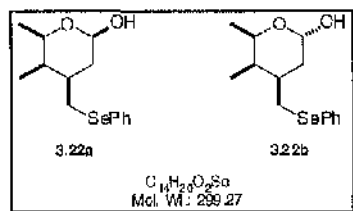
lactols **3.22a,b** to sulfones **3.23a,b**

To the crude mixture of lactols **3.22a,b** in CH_2Cl_2 (5 ml) was added CaCl_2 anhydrous (255 mg, 2.5 mmol) followed by freshly prepared benzenesulfinic acid (142 mg, 1.0 mmol). After 15 h at room temperature, the reaction mixture was diluted (10 ml), filtered and washed with saturated NaHCO_3 . The aqueous layer was then extracted with CH_2Cl_2 (3 x 10 ml) and the combined organic layers were dried (MgSO_4) and concentrated *in vacuo* to give a crude mixture of inseparable diastereomeric sulfones **3.23a,b** (404 mg, 0.96 mmol, 96%) which was used directly in the next step.

sulfones 3.23a,b to tributylstannane 2.3

To the crude mixture of sulfones **3.23a,b** in THF (5 ml) was added dropwise at -78°C $n\text{BuLi}$ (0.72 ml, 1.40 M in hexanes, 1.0 mmol). After 30 min at -78°C , Bu_3SnCl (0.27 ml, 1.0 mmol) was added slowly and the reaction mixture was stirred at -78°C for 1 h and at -10°C for 2 h. The solution was evaporated to dryness and taken up in chloroform (7 ml). DIPEA (0.19 ml, 1.5 mmol) was added and the resulting mixture was heated at 70°C for 4 h, then cooled to room temperature, and then concentrated *in vacuo*. Purification by column chromatography (deactivated Al_2O_3 (5% H_2O), 500 g, column diameter = 8 cm, 1% Et_3N in hexanes) gave 373 mg (0.65 mmol, 65% over 3 steps) of stannane **2.3**.

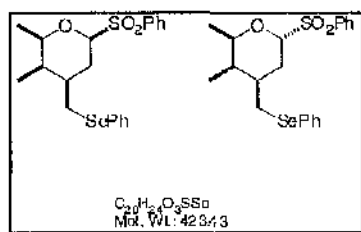
(2*R*,4*R*,5*R*,6*R*)-5,6-Dimethyl-4-phenylselanylmethyl-tetrahydro-pyran-2-ol (**3.22a**) and (2*S*,4*R*,5*R*,6*R*)-5,6-Dimethyl-4-phenylselanylmethyl-tetrahydro-pyran-2-ol (**3.22b**)



Data for the crude mixture of lactols **3.22a** and **3.22b** are reported using M for the major diastereomer **3.22a** and m for the minor diastereomer **3.22b**.

ν_{max} film/ cm^{-1} 3398, 2972, 2928, 2890, 1725, 1578, 1477, 1437, 1383; δ_{H} (400 MHz, CDCl_3): 7.46-7.39 (2H_{M} and 2H_{m} , m, Harom), 7.22-7.14 (3H_{M} and 3H_{m} , m, Harom), 5.20 (1H_{m} , d, J 3.5, C6-H), 4.61 (1H_{M} , dd, J 9.4, 1.6, C6- H_{m}), 4.14 (1H_{m} , dq, J 6.4, 2.1, C2-H), 4.00 (1H_{M} , bd s, OH), 3.53 (1H_{M} , dq, J 6.4, 2.1, C2-H), 3.18 (1H_{m} , br, OH), 2.85-2.71 (2H_{M} and 2H_{m} , m, 2 x Se- CH_2), 2.33-2.23 (1H_{m} , m, 10 lines, C4-H), 1.91-1.80 (1H_{M} , m, 10 lines, C4-H), 1.77 (1H_{M} , app dt, J 12.8, 2.7, C5- $\text{H}_{\text{A}}\text{H}_{\text{B}}$), 1.73-1.68 (1H_{m} , m, C3-H), 1.64-1.57 (1H_{m} , m, C5- $\text{H}_{\text{A}}\text{H}_{\text{B}}$), 1.64-1.57 (1H_{M} , m, C3-H), 1.43 (1H , app dt, J 13.3, 3.8, C5-H), 1.26 (1H , dd, J 12.8, 6.6, C5-H), 1.26 (1H_{M} , dd, J 12.8, 6.6, C5- $\text{H}_{\text{A}}\text{H}_{\text{B}}$), 1.10 (3H_{M} , d, J 6.5, C2-Me), 1.03 (3H_{m} , d, J 6.5, C2-Me), 0.73 (3H_{M} , d, J 7.0, C3-Me), 0.69 (3H_{m} , d, J 7.0, C3-Me); δ_{C} (100 MHz, CDCl_3) 132.5 (1, 2C_{M} + 2C_{m} , Carom), 129.3 (0, 1C_{m} , Carom), 129.2 (0, 1C_{M} , Carom), 129.05 (1, 2C_{M} , Carom), 128.99 (1, 2C_{m} , Carom), 126.8 (1, 1C_{M} , Carom), 126.7 (1, 1C_{M} , Carom), 96.2 (1, 1C_{M} , C6), 91.6 (1, 1C_{m} , C6), 74.4 (1, 1C_{M} , C2), 67.6 (1, 1C_{M} , C2), 38.6 (1, 1C_{M} , C4), 35.7 (1, 1C_{m} , C3), 35.4 (1, 1C_{M} , C3), 33.9 (2, 1C_{M} , C5), 33.7 (1, 1C_{m} , C4), 32.5 (1, 1C_{m} , Se- CH_2), 31.9 (2, 1C_{M} , Se- CH_2), 31.0 (2, 1C_{M} , C5), 18.5 (3, 1C_{m} , C2-Me), 18.3 (3, 1C_{M} , C2-Me), 5.0 (3, 1C_{M} , C3-Me), 4.0 (3, 1C_{m} , C3-Me), m/z (EI) 302 (20), 301 (20), 300 [M^+ , 100%], 299 (10), 298 (55), 297 (20), 296 (20), 295 (5), 157 (65), 143 (80); Found: (EI), 300.0628. $\text{C}_{14}\text{H}_{20}\text{O}_2\text{Se}$ requires M , 300.0629.

(2*R*,3*R*,4*R*,6*S*)-6-Benzenesulfonyl-2,3-dimethyl-4-phenylselenanylmethyl-tetrahydro-pyran (3.23a) and (2*R*,3*R*,4*R*,6*R*)-6-Benzenesulfonyl-2,3-dimethyl-4-phenylselenanylmethyl-tetrahydro-pyran (3.23b)

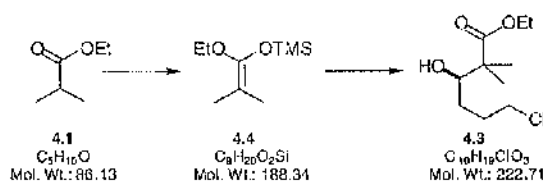


1H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) data of the mixture of sulfones **3.23a** and **3.23b** are reported here describing only the best resolved and characteristic pics M for the major diastereomer **3.23a** and m for the minor diastereomer **3.23b**.

ν_{max} film/ cm^{-1} 3527, 3058, 2973, 1726, 1578, 1477, 1445, 1384; δ_H (400 MHz, $CDCl_3$): 4.63 (1H_m, d, J 7.6, C6-H), 4.58 (1H_m, dq, J 6.5, 4.3, C2-H), 4.29 (1H_M, dd, J 11.7, 2.8, C6-H), 3.43 (1H_M, dq, J 6.4, 2.0, C2-H), 1.04 (3H_M, d, J 6.5, C2-Me), 0.98 (3H_m, d, J 6.5, C2-Me), 0.66 (3H_M, d, J 7.0, C3-Me), 0.53 (3H_m, d, J 7.0, C3-Me); δ_C (100 MHz, $CDCl_3$) 138-127 (24C, Carom), 91.3 (1, 1C_M, C6), 89.6 (1, 1C_m, C6), 78.6 (1, 1C_M, C2), 72.8 (1, 1C_M, C2), 39.3 (1, 1C_M + 1C_m, C4), 35.4 (1, 1C_M, C3), 34.9 (1, 1C_m, C3), 32.5 (2, 1C_m, C5), 31.8 (2, 1C_M, C5), 24.8 (1, 1C_M, Se-CH₂), 22.7 (2, 1C_m, Se-CH₂), 18.6 (3, 1C_m, C2-Me), 18.3 (3, 1C_M, C2-Me), 4.8 (3, 1C_M, C3-Me), 3.9 (3, 1C_m, C3-Me), m/z (CI, NH_4) 444 (7), 443 (5), 442 [(M+ NH_4)⁺, 25%] 441 (5), 440 (15), 439 (5), 438 (6), 286 (5), 285 (20), 284 (18), 283 (100), 282 (10), 281 (50), 280 (20), 279 (20); Found: (EI), 424.0604. $C_{20}H_{24}O_3SSe$ requires M , 424.0612.

10.3 Synthesis of enone 2.4

Ethyl (*R*)-6-chloro-3-hydroxy-2,2-dimethylhexanoate (**4.3**)



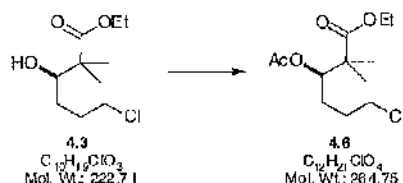
By directed aldol condensation:

A solution of $BH_3 \cdot THF$ complex (313 ml, 1 M in THF, 313 mmol) was added dropwise to a stirred suspension of (*S*)-*N*-tosylvaline¹³² (105.3 g, 388 mmol) in CH_2Cl_2 (1.85 l) under nitrogen at rt over 30 min. After 30 min, the clear solution was cooled to $-70^\circ C$ and a solution of 4-chlorobutanal¹³³ (41.4 g, 388 mmol) in CH_2Cl_2 (35 ml) was added over 10 min. Silyl ketene acetal **4.4**¹³⁴ (78.9 g, 419 mmol) was then added over 30 min maintaining the reaction temperature below $-65^\circ C$. After 2 h at $-70^\circ C$ a solution of NaOH (24.5 g, 612 mmol) in 300 ml of water was added and the reaction mixture was allowed to warm to rt. The phases were separated, the aqueous phase was extracted with CH_2Cl_2 (2 x 100 ml) and the combined organic extracts were washed with water (500 ml) and concentrated *in vacuo*. The residue was treated with water (500 ml) and extracted with Et_2O (4 x 200 ml). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to give the hydroxy ester **4.3** (97.7 g, 370 mmol, 95%) as a yellow oil. The enantiomeric ratio (97:3) had been determined by integration of the 1H NMR signals at δ 1.16 (major) and δ

1.11 (minor) of the (*R*)-MTPA esters prepared from **4.3** in the usual way (270 MHz, C₆D₆, referenced to 7.16 ppm).⁷⁷

Spectroscopic data (¹H NMR, ¹³C NMR, IR, and [α]_D) in agreement with Dr C. Smith data.⁷⁷

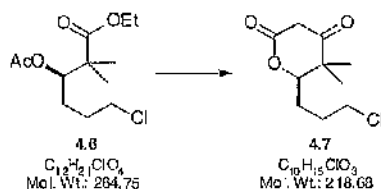
Ethyl (*R*)-3-acetoxy-6-chloro-2,2-dimethylhexanoate (**4.6**)



To a solution of the crude hydroxy ester **4.3** (97.7 g, 370 mmol), triethylamine (76 ml, 550 mmol), and DMAP (233 mg, 1.9 mmol) in CH₂Cl₂ (300 ml) was added acetic anhydride (49 ml, 517 mmol) dropwise. The solution was stirred overnight at rt and then diluted with hexanes (1 l), washed with water (3 x 200 ml), and brine (100 ml), dried (Na₂SO₄) and concentrated *in vacuo*. The crude product was filtered through a pad of silica gel (15 g, 10% Et₂O in hexanes), concentrated *in vacuo* and the residue distilled (bp 88–96 °C, 0.01 mm/Hg) to give acetate **4.6** (78.2 g, 0.295 mol, 76%) as a colourless oil.

Spectroscopic data (¹H NMR, ¹³C NMR, IR, and [α]_D) in agreement with Dr C. Smith data.⁷⁷

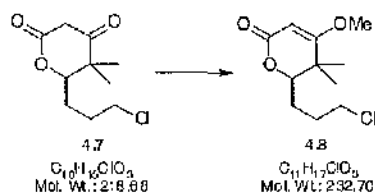
(*R*)-6-(3-Chloropropyl)-5,5-dimethyl-dihydro-pyran-2,4-dione (**4.7**)



BuLi (293 ml, 2.32M in hexane, 610 mmol) was added to a stirred solution of diisopropylamine (90 ml, 637 mmol) in THF (875 ml) at 0 °C over 15 min. After stirring at 0 °C for 20 min, the solution was cooled to –74 °C and a solution of the ester acetate **4.6** (78.2 g, 292 mmol) in THF (125 ml) was added dropwise over 15 min keeping the temperature of the reaction mixture below –68 °C. The yellow solution was stirred at –74 °C for 1.5 h before adding aqueous HCl (2 M, 750 ml). The phases were separated and the aqueous phase was extracted with CH₂Cl₂ (3 x 240 ml). The combined organic extracts were washed with brine (200 ml), dried (Na₂SO₄) and concentrated *in vacuo*. The residue was recrystallised twice from hexanes–Et₂O to give the β-ketolactone **4.7** (50 g, 228 mmol, 78%) as a white solid: mp 103–105 °C.

Spectroscopic data (¹H NMR, ¹³C NMR, IR, and [α]_D) in agreement with Dr C. Smith data.⁷⁷

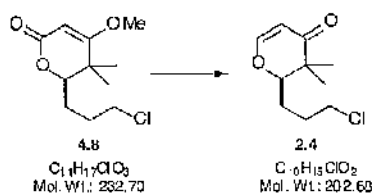
(R)-6-(3-Chloropropyl)-4-methoxy-5,5-dimethyl-5,6-dihydro-pyran-2-one (4.8)



Potassium carbonate (4.74 g, 34.4 mmol) was added to a solution of β -ketolactone **4.7** (5.00 g, 22.9 mmol), 18-crown-6 (60 mg, 0.25 mmol) and dimethyl sulfate (2.6 ml, 27.5 mmol) in CH_2Cl_2 (50 ml). The reaction mixture was vigorously stirred at rt for 20 h, filtered through a pad of Celite and concentrated *in vacuo*. Kugelrohr distillation (bp 245–250°(oven)/0.05 mm Hg) gave enol ether **4.8** (5.28 g, 22.7 mmol, 99%) as a colourless oil which formed a white solid on cooling; mp 56–57 °C.

Spectroscopic data (1H NMR, ^{13}C NMR, IR, and $[\alpha]_D$) in agreement with Dr C. Smith data.⁷⁷

(R)-6-(3-Chloropropyl)-5,6-dihydro-5,5-dimethyl-4H-pyran-4-one (2.4)

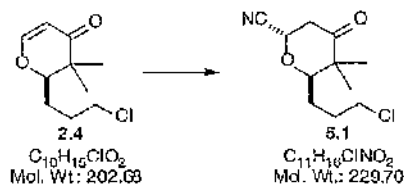


DIBAL-H (neat, 8.7 ml, 48.6 mmol) was added dropwise to a stirred solution of lactone **4.8** (10.3 g, 44.2 mmol) in CH_2Cl_2 (80 ml) maintaining the temperature of the reaction mixture below –70 °C. The reaction mixture was stirred at –70 °C for 40 min and then poured onto aqueous HCl (2M, 250 ml) and vigorously stirred at rt for 15 min. The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 30 ml). The combined organic extracts were washed with saturated aqueous $NaHCO_3$, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was distilled to give enone **2.4** (7.6 g, 37.4 mmol, 85%) as a colourless oil; bp 110–112 °C/0.8 mm Hg.

Spectroscopic data (1H NMR, ^{13}C NMR, IR, and $[\alpha]_D$) in agreement with Dr C. Smith data.⁷⁷

10.4 Synthesis of Pederin (1.1)

(2S,6R)-6-(3-Chloropropyl)-2-cyano-tetrahydro-5,5-dimethyl-2H-pyran-4-one (5.1)



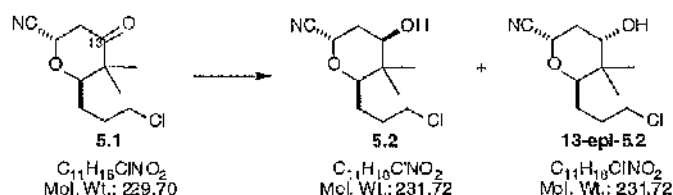
Trimethylsilyl trifluoromethanesulfonate (110 μ l, 0.6 mmol) was added to a stirred solution of dihydropyranone **2.4** (4.0 g, 19.7 mmol) and trimethylsilyl cyanide (2.7 ml, 21.7 mmol) in CH_2Cl_2 (40 ml) at

0 °C. The reaction mixture was stirred for 1.5 h at 0 °C and poured onto saturated aqueous NaHCO₃ (10 ml). The phases were separated and the aqueous phase was extracted with CH₂Cl₂ (2 x 20 ml). The combined organic extracts were dried (MgSO₄) and concentrated *in vacuo*. The residue was treated with THF (10 ml) and aqueous HCl (2M, 2 ml) and then stirred at rt for 30 min. The reaction mixture was extracted with CH₂Cl₂ (3 x 25 ml). The combined organic extracts were dried (MgSO₄) and concentrated *in vacuo*. Kugelrohr distillation [bp 250 °C(oven)/0.05 mm Hg] gave a colourless oil which crystallised upon cooling in the refrigerator. Recrystallisation from hexanes–Et₂O gave cyano ketone **5.1** (4.15 g, 18.1 mmol, 92%) as a white solid: mp 36–38 °C; [α]_D²⁰ +120.0 (c 1.0, CHCl₃); ν_{\max} film/cm⁻¹ 1715; δ_{H} (400 MHz, CDCl₃): 5.18 (1H, dd, *J* 8.1, 1.5, C11H), 3.79 (1H, dd, *J* 8.8, 3.7, C15H), 3.62 (2H, t, *J* 6.6, C18H₂), 3.10 (1H, dd, *J* 15.5, 8.1, C12H_AH_B), 2.57 (1H, dd, *J* 15.5, 2.2, C12H_AH_B), 2.12–2.01 (1H, m, C17H_AH_B), 1.93–1.82 (1H, m, C17H_AH_B), 1.77–1.70 (2H, m, C16H₂), 1.16 (3H, s, C14Me), 1.12 (3H, s, C14Me); δ_{C} (100 MHz, CDCl₃): 206.4 (0, C13), 116.7 (0, C10), 81.4 (1, C15), 64.5 (1, C11), 50.1 (0, C14), 44.7 (2, C18), 40.1 (2, C12), 29.2 (2, C17), 26.0 (2, C16), 18.9 (3, 2C, C14Me); *m/z* (EI): 231 (10), 229 (M⁺, 30), 123 (87), 70 (100%). Found: (M⁺), 229.0867. C₁₁H₁₆O₂NCI requires *M*, 229.0870. Found: C, 57.32; H, 6.95; N, 5.96%. C₁₁H₁₆ClNO₂ requires C, 57.52; H, 7.02; N, 6.10.

(2*S*,4*R*,6*R*)-6-(3-Chloropropyl)-2-cyano-tetrahydro-5,5-dimethyl-2*H*-pyran-4-ol (**5.2**)

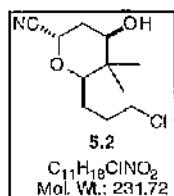
and

(2*S*,4*S*,6*R*)-6-(3-Chloropropyl)-2-cyano-tetrahydro-5,5-dimethyl-2*H*-pyran-4-ol (epi-**5.2**)



To a solution of ketone **5.1** (13 g, 56.6 mmol) and CeCl₃•7H₂O (10.4 g, 28.0 mmol) in MeOH (130 ml) at –95 °C was added in one portion sodium borohydride (6.5 g, 169.7 mmol). The reaction mixture was stirred for 1 h below –85 °C and was then allowed to warm to –60 °C over 1 h with stirring before pouring onto aqueous HCl (2 M, 150 ml) at 0 °C. The phases were separated and the aqueous phase was extracted with CH₂Cl₂ (3 x 150 ml). The combined organic extracts were washed with saturated aqueous NaHCO₃ (35 ml), dried (Na₂SO₄) and concentrated *in vacuo*. The residue was filtered through a pad of SiO₂ to give a 30:1 mixture of alcohols (13.0 g, >99%) as a white solid. Purification by column chromatography (SiO₂, 10% Et₂O in CH₂Cl₂) gave pure undesired alcohol epi-**5.2** (110 mg, 0.48 mmol, 0.8%) and 12.8 g of a mixture of **5.2** and epi-**5.2** which was recrystallised from hexanes–Et₂O to give pure alcohol **5.2** (10.1 g, 43.6 mmol, 77%) as white crystals:

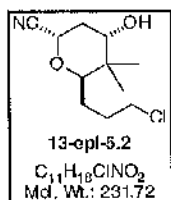
(2*S*,4*R*,6*R*)-6-(3-Chloropropyl)-2-cyano-tetrahydro-5,5-dimethyl-2*H*-pyran-4-ol (**5.2**)



mp 71–72 °C; [α]_D²⁷ +83.0 (c 1.0, CHCl₃); ν_{\max} (CCl₄)/cm⁻¹ 3630, 3540; δ_{H} (400 MHz, CDCl₃): 4.91 (1H, dd, *J* 5.9, 1.5, C11H), 3.75 (1H, dd, *J* 11.0, 5.1, C13H), 3.67–3.53 (2H, m, C18H₂), 3.42 (1H, dd, *J* 10.3,

1.5, C15H), 2.01 (1H, ddd, J 13.5, 11.7, 6.0, C12H_AH_B), 1.94 (1H, ddd, J 13.5, 4.9, 1.5, C12H_AH_B), 2.05–1.90 (1H, m, C17H_AH_B), 1.73–1.87 (2H, m, C16H_AH_B and C17H_AH_B), 1.67 (1H, br s, C13OH), 1.60–1.48 (1H, m, C16H_AH_B), 1.02 (3H, s, C14Me), 0.88 (3H, s, C14Me); δ_C (100 MHz, CDCl₃): 117.8 (0, C10), 81.1 (1, C15), 71.9 (1, C13), 64.0 (1, C11), 44.9 (2, C18), 39.4 (0, C14), 32.7 (2, C12), 29.4 (2, C17), 25.7 (2, C16), 22.2 (3, C14Me), 12.0 (3, C14Me); m/z (CI, NH₃) 249 [(M+NH₄)⁺, 100%]. Found: C, 56.87; H, 7.70; N, 6.03; Cl 15.35%. C₁₁H₁₈ClNO₂ requires C, 56.97; H, 7.76; N, 6.04; Cl 15.32.

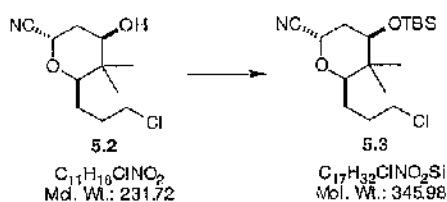
(2S,4S,6R)-6-(3-chloropropyl)-2-cyano-tetrahydro-5,5-dimethyl-2H-pyran-4-ol (13-epi-5.2)



The minor isomer (**epi-5.2**) was isolated as a colourless oil: $[\alpha]_D^{20} +84.2$ (c 1.3, CHCl₃); ν_{\max} (film)/cm⁻¹ 3491, 2964; δ_H (400 MHz, CDCl₃): 4.77 (1H, d, J 6.7, C11H), 3.95 (1H, dd, J 10.7, 1.2, C15H), 3.61–3.54 (3H, m, C13H and C18H₂), 2.32–2.25 (2H, m, OH and C12H_AH_B), 2.04–1.94 (1H, m, C17H_AH_B), 1.89–1.78 (2H, m, C17–H_AH_B), 1.70–1.61 (1H, m, C16H_AH_B), 1.50–1.39 (1H, m, C16H_AH_B), 0.98 (3H, s, C14Me), 0.90 (3H, s, C14Me); δ_C (100 MHz, CDCl₃): 119.4 (0, C10), 75.1 (1, C15), 72.2 (1, C13), 60.7 (1, C11), 45.0 (2, C18), 36.9 (0, C14), 31.5 (2, C12), 29.2 (2, C17), 25.6 (2, C16), 22.7 (3, C14Me), 19.0 (3, C14Me); m/z (CI, NH₃) 249 [(M+NH₄)⁺, 100%]. Found: (M+NH₄)⁺, 249.1368. C₁₁H₁₈O₂N₂Cl requires M , 249.1370. Found: C, 56.96; H, 7.74; N, 6.01%. C₁₁H₁₈ClNO₂ requires C, 56.97; H, 7.76; N, 6.04.

The isomers are easily separable on TLC (CH₂Cl₂–Et₂O 9:1) R_f (major isomer) 0.39: R_f (minor isomer) 0.47.

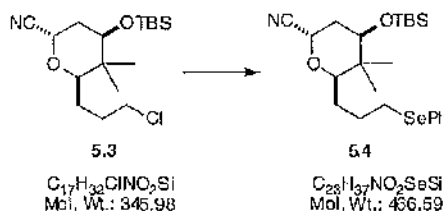
(2S,4R,6R)-4-(tert-Butyldimethylsilyloxy)-6-(3-chloropropyl)-2-cyano-tetrahydro-5,5-dimethyl-2H-pyran (5.3)



tert-Butyldimethylsilyl trifluoromethanesulfonate (3.85 ml, 16.6 mmol) was added dropwise to a stirred solution of alcohol **5.2** (3.5 g, 15.1 mmol) and 2,6-lutidine (3.67 ml, 18.2 mmol) in dry CH₂Cl₂ (25 ml) at 0 °C. The reaction mixture was stirred at 0–5 °C for 2.5 h, then poured into saturated aqueous NaHCO₃ (10 ml). The phases were separated and the aqueous phase was extracted with CH₂Cl₂ (2 x 30 ml). The combined organic extracts were washed with aqueous HCl (2M, 70 ml) followed by water (90 ml), dried (Na₂SO₄) and concentrated *in vacuo*. The residue was purified by column chromatography (SiO₂, 10% Et₂O in hexanes) to give silyl ether **5.3** as a white solid (5.20 g, 15.0 mmol, >99%); mp 44–46 °C (hexanes–Et₂O); $[\alpha]_D^{20} +60.7$ (c 1.84, CHCl₃); ν_{\max} (CCl₄)/cm⁻¹ 2958, 2932, 2858, 1472, 1258, 1084, 876, 838; δ_H (400 MHz, CDCl₃): 4.87 (1H, dd, J 5.9, 1.5, C11H), 3.67 (1H, dd, J 11.8, 5.2, C13H), 3.65–3.53 (2H, m, C18H₂), 3.43 (1H, dd, J 10.3, 1.5, C15H), 2.08–1.91 (2H, m), 1.89–1.69 (3H, m), 1.60–1.44 (1H, m), 0.93

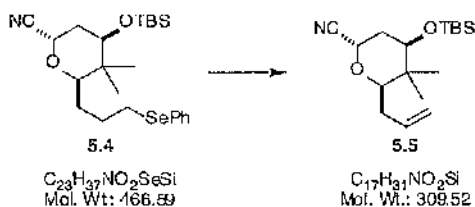
(3H, s, C14Me), 0.90 (9H, s, ^tBuSi), 0.85 (3H, s, C14Me), 0.09 (3H, s, SiMe), 0.08 (3H, s, SiMe); δ_C (100 MHz, CDCl₃): 117.9 (0, C10), 81.2 (1, C15), 72.5 (1, C13), 63.9 (1, C11), 44.9 (2, C18), 40.0 (0, C14), 33.7 (2, C12), 29.5 (2, C17), 26.0 (2, C16), 25.9 (3, 3C, ^tBuSi), 22.8 (3, C14Me), 18.1 (0, CSi), 12.4 (3, C14Me), -4.0 (3, MeSi), -4.8 (3, MeSi); m/z (CI, NH₃) 363 [(M+NH₄)⁺, 100%]. Found: C, 58.97; H, 9.24; N, 3.99; Cl 10.26%. C₁₇H₃₂ClNO₂Si requires C, 58.97; H, 9.26; N, 4.04; Cl 10.26.

(2S,4R,6R)-4-(*tert*-Butyldimethylsilyloxy)-2-cyano-6-(3-phenylselenenylpropyl)-5,5-dimethyl-tetrahydro-2H-pyran (5.4)



Sodium borohydride (720 mg, 18.7 mmol) was added portionwise to a stirred suspension of diphenyl diselenide (2.65 g, 8.46 mmol) in dry ethanol (25 ml). The exothermic reaction resulted in a pale yellow solution to which was added chloride **5.3** (4.5 g, 13 mmol). The resulting mixture was refluxed for 1 h, cooled to rt and treated with aqueous NaOH (2M, 40 ml) and extracted with hexanes (3 x 20 ml). The combined organic extracts were dried (Na₂SO₄) and concentrated *in vacuo*. The residue was purified by chromatography on SiO₂ eluting with toluene:hexanes (1:1) until the yellow band passed and then hexanes–Et₂O (85:15) to give selenide **5.4** (5.5 g, 91%) as a colourless oil that crystallised on standing; mp 28–30 °C (hexanes–Et₂O); $[\alpha]_D^{20} +36.9$ (c 1.89, CHCl₃); ν_{\max} (CCl₄)/cm⁻¹ 2958, 2932, 2858, 1595, 1472, 1258, 1084, 876, 838; δ_H (360 MHz, CDCl₃): 7.57–7.50 (2H, m), 7.35–7.20 (3H, m), 4.85 (1H, dd, *J* 6.0, 1.3, C11H), 3.67 (1H, dd, *J* 11.5, 4.6, C13H), 3.42 (1H, dd, *J* 10.3, 1.4, C15H), 3.02–2.90 (2H, m, C18H₂), 1.99 (1H, ddd, *J* 13.6, 11.6, 6.1, C12H_AH_B), 2.00–1.88 (1H, m), 1.85–1.64 (3H, m), 1.56–1.43 (1H, m), 0.93 (9H, s, ^tBuSi), 0.91 (3H, s, C14Me), 0.84 (3H, s, C14Me), 0.11 and 0.10 (3H each, s, Me₂Si); δ_C (90 MHz, CDCl₃): 132.4 (1, 2C), 130.4 (0), 129.0 (1, 2C), 126.6 (1), 117.8 (0), 81.1 (1), 72.4 (1), 63.7 (1), 39.8 (0), 33.6 (2), 28.5 (2), 27.5 (2), 27.0 (2), 25.8 (3, 3C), 22.6 (3), 17.9 (0), 12.3 (3), -4.2 (3), -4.9 (3); m/z (CI, NH₃) 485 [(M+NH₄)⁺, 100%], 483 (50). Found: C, 59.29; H, 8.03; N, 2.92%. C₂₃H₃₇NO₂SeSi requires C, 59.15; H, 7.92; N, 3.00.

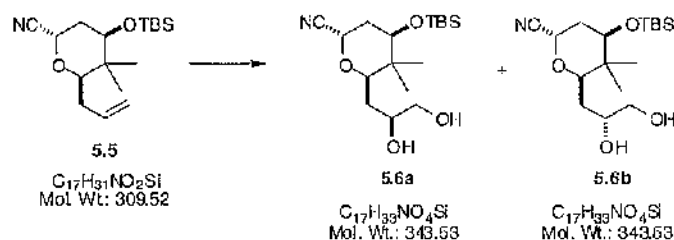
(2S,4R,6R)-4-(*tert*-Butyldimethylsilyloxy)-2-cyano-tetrahydro-5,5-dimethyl-6-(prop-2-enyl)-2H-pyran (5.5)



Sodium metaperiodate (2.15 g, 10 mmol) was added in one portion to a stirred solution of selenide **5.4** (3.15 g, 6.75 mmol) in water (100 ml) and methanol (200 ml). The reaction mixture was stirred for 30 min, extracted with CH₂Cl₂ (3 x 50 ml). The combined organic phases were dried (Na₂SO₄), triethylamine (0.5 ml, 7.1 mmol) was added to the solution and the mixture then concentrated under high vacuum at rt. Toluene (25 ml) was added to the residue followed by the addition of triethylamine (10.5 ml, 75 mmol). The reaction

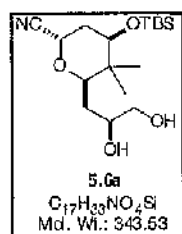
mixture was then refluxed for 30 min. Solvent was removed *in vacuo* and the residue purified by column chromatography (SiO₂, 10% toluene in hexanes) followed by Kugelrohr distillation [bp 200 °C (oven)/0.05 mmHg] to give the olefin **5.5** (2.0 g, 6.46 mmol, 96%) as a colourless oil: $[\alpha]_D^{20} +48.6$ (c 1.35, CHCl₃); ν_{\max} film/cm⁻¹ 1644, 1472, 1258, 1162, 1104, 1082, 880, 838, 776; δ_H (400 MHz, CDCl₃): 5.84 (1H, ddt, *J* 16.8, 10.2, 6.8, C17H), 5.10 (1H, dq, *J* 16.8, 1.5, C18H_AH_B), 5.07 (1H, dq, *J* 10.2, 1.5, C18H_AH_B), 4.87 (1H, dd, *J* 6.0, 1.5, C11H), 3.68 (1H, dd, *J* 11.4, 4.6, C13H), 3.54 (1H, dd, *J* 10.0, 2.5, C15H), 2.33 (1H, dddt, *J* 15.0, 6.2, 2.5, 1.5, C16H_AH_B), 2.17 (1H, dddt, *J* 15.0, 9.8, 6.8, 1.3, C16H_AH_B), 2.00 (1H, ddd, *J* 13.7, 11.6, 6.0, C12H_AH_B), 1.78 (1H, ddd, *J* 13.7, 4.6, 1.6, C12H_AH_B), 0.94 (3H, s, C14Me), 0.90 (9H, s, ^{*t*}BuSi), 0.86 (3H, s, C14Me), 0.09 and 0.08 (3H each, s, Me₂Si); δ_C (90 MHz, CDCl₃): 135.7 (1, C17), 117.9 (0, C10), 116.6 (2, C18), 81.6 (1, C15), 72.5 (1, C13), 64.0 (1, C11), 40.0 (0, C14), 33.8 (2, C12), 33.5 (2, C16), 25.9 (3, 3C, ^{*t*}BuSi), 22.9 (3, C14Me), 18.1 (0, CSi), 12.6 (3, C14Me), -4.0 (3, MeSi), -4.8 (3, MeSi); *m/z* (CI, NH₃) 327 [(M+NH₄)⁺, 100%]. Found: C, 66.15; H, 10.09; N, 4.62%. C₁₇H₃₁NO₂Si requires C, 66.02; H, 10.03; N, 4.53.

Asymmetric dihydroxylation of alkene **5.5**



Alkene **5.5** (1.4 g, 4.5 mmol) and dihydroquinine 9-phenanthryl ether¹⁰⁴ (113 mg, 0.225 mmol) were stirred in warm *t*-BuOH (28 ml) until the crystals of ligand dissolved completely. After cooling to rt, water (28 ml), K₃Fe(CN)₆ (4.5 g, 13.5 mmol) and K₂CO₃ (1.90 g, 13.5 mmol) were added and the mixture was cooled to 0 °C before addition of potassium osmate dihydrate (89 mg, 0.225 mmol). The reaction mixture was stirred for 3 h at 0 °C, then treated with saturated aqueous Na₂SO₃ (40 ml) and extracted with CH₂Cl₂ (80 + 2 x 40 ml). The combined organic extracts were washed with brine (30 ml), dried (MgSO₄) and concentrated *in vacuo* to give the crude diols **5.6a,b** as a 1.5:1 mixture of diastereoisomers. The residue was purified by column chromatography on SiO₂ (70 g, 0–1.4% MeOH in CH₂Cl₂) to give pure diol **5.6a** (806 mg, 2.34 mmol, 52%) and pure diol **5.6b** (402 mg, 1.2 mmol, 26%).

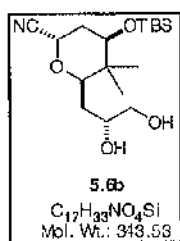
(2*S*,4*R*,6*R*)-4-(*tert*-Butyldimethylsilyloxy)-2-cyano-6-[(2*S*)-2,3-dihydroxypropyl]-tetrahydro-5,5-dimethyl-2*H*-pyran (**5.6a**)



gave mp 53–55 °C (hexanes–Et₂O); $[\alpha]_D^{25} +50.0$ (c 2.0, CHCl₃); ν_{\max} film/cm⁻¹ 3442, 1472, 1258, 1100, 1082, 878; δ_H (400 MHz, CDCl₃): 4.90 (1H, dd, *J* 6.0, 0.9, C11H), 3.96–3.90 (1H, m, C17H), 3.73–3.63 (3H, m (10 lines), C13H + C15H + C18H_AH_B), 3.51 (1H, dd, *J* 11.1, 6.0, C18H_AH_B), 2.00 (1H, ddd, *J* 13.7,

11.6, 6.1, $C_{12}H_AH_B$), 1.81 (1H, ddd, J 13.7, 4.6, 1.3, $C_{12}H_AH_B$), 1.78–1.64 (2H, m, $C_{16}H_2$), 1.64–1.40 (2H, br s, $C_{17}OH$ and $C_{18}OH$), 0.91 (3H, s, $C_{14}Me$), 0.89 (9H, s, tBu), 0.86 (3H, s, $C_{14}Me$), 0.08 (3H, s, $SiMe$), 0.07 (3H, s, $SiMe$); δ_C (100 MHz, $CDCl_3$): 117.6 (0, C_{10}), 81.0 (1, C_{13} or C_{15} or C_{17}), 72.2 (1, C_{13} or C_{15} or C_{17}), 71.1 (1, C_{13} or C_{15} or C_{17}), 65.8 (2, C_{18}), 63.8 (1, C_{11}), 39.8 (0, C_{14}), 33.4 (2, C_{16} or C_{12}), 32.1 (2, C_{12} or C_{16}), 25.7 (3, 3C, $tBuSi$), 22.6 (3, $C_{14}Me$), 17.9 (0, CSi), 12.3 (3, $C_{14}Me$), -4.2 (3, $MeSi$), -5.0 (3, $MeSi$); m/z (CI, NH_3): 361 [($M+NH_4$) $^+$, 100%], 343 [($M+H$) $^+$, 8], 329 (12), 96 (12). Found: ($M+H$) $^+$, 344.2258. $C_{17}H_{34}O_4NSi$ requires M , 344.2257.

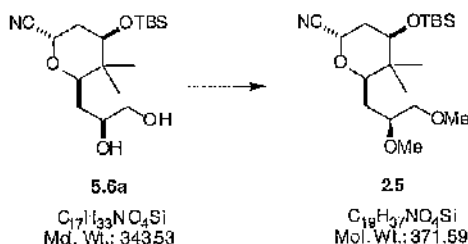
(2*S*,4*R*,6*R*)-4-(*tert*-Butyldimethylsilyloxy)-2-cyano-6-[(2*R*)-2,3-dihydroxypropyl]-tetrahydro-5,5-dimethyl-2*H*-pyran (5.6b)



mp 36–38 °C ($CHCl_3$); $[\alpha]_D^{25} +58.5$ (c 1.0, $CHCl_3$); ν_{max} KBr/cm^{-1} 3426, 1471, 1257, 1103, 1083, 881; δ_H (400 MHz, $CDCl_3$): 4.86 (1H, dd, J 6.0, 0.9, $C_{11}H$), 3.92–3.85 (1H, m, $C_{17}H$), 3.74 (1H, dd, J 10.3, 1.3, $C_{15}H$), 3.70 (1H, dd, J 11.6, 4.7, $C_{13}H$), 3.65 (1H, dd, J 11.1, 3.3, $C_{18}H_AH_B$), 3.51 (1H, dd, J 10.8, 7.2, $C_{18}H_AH_B$), 2.00 (1H, ddd, J 13.6, 11.6, 6.1, $C_{12}H_AH_B$), 1.79 (1H, ddd, J 13.6, 4.6, 1.4, $C_{12}H_AH_B$), 1.67 (1H, ddd, J 14.4, 8.9, 1.6, $C_{16}H_AH_B$), 1.67 (1H, ddd, J 14.4, 10.3, 3.6, $C_{16}H_AH_B$), 1.60–1.40 (2H, br s, $C_{17}OH$ and $C_{18}OH$), 0.92 (3H, s, $C_{14}Me$), 0.90 (9H, s, tBu), 0.84 (3H, s, $C_{14}Me$), 0.09 (3H, s, $SiMe$), 0.08 (3H, s, $SiMe$); δ_C (100 MHz, $CDCl_3$): 117.7 (0, C_{10}), 78.1 (1, C_{13} or C_{15}), 72.3 (1, C_{15} or C_{13}), 69.2 (1, C_{17}), 66.8 (2, C_{18}), 66.8 (1, C_{11}), 39.6 (0, C_{14}), 33.5 (2, C_{16} or C_{12}), 32.2 (2, C_{12} or C_{16}), 25.7 (3, 3C, $tBuSi$), 22.5 (3C, $C_{14}Me$), 17.9 (0, CSi), 12.3 (3, $C_{14}Me$), -4.2 (3, $MeSi$), -5.0 (3, $MeSi$); m/z (CI, NH_3) 361 [($M+NH_4$) $^+$, 100%], 343 [($M+H$) $^+$, 15], 329 (25), 96 (62). Found: ($M+H$) $^+$, 344.2258. $C_{17}H_{34}O_4NSi$ requires M , 344.2257.

Neither **5.6a** nor **5.6b** gave satisfactory microanalytical data.

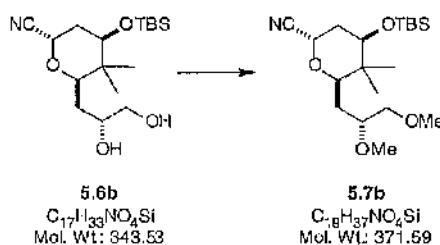
(2*S*,4*R*,6*R*)-4-(*tert*-Butyldimethylsilyloxy)-2-cyano-6-[(2*S*)-2,3-dimethoxypropyl]-tetrahydro-5,5-dimethyl-2*H*-pyran (2.5)



NaH (310 mg, 7.7 mmol, 60% in oil) was added in one portion to diol **5.6a** (870 mg, 2.53 mmol), MeI (0.79 ml, 12.6 mmol) and 18-crown-6 (80 mg, 0.30 mmol) in THF (24 ml) at 0 °C. The ice bath was removed and the reaction mixture was sealed and stirred at rt for 24 h. The reaction mixture was then poured onto saturated

aqueous NH_4Cl (5 ml), extracted with CH_2Cl_2 (3 x 25 ml) and the combined organic extracts were dried (MgSO_4) and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2 , 50 g, 20% Et_2O in hexanes) to give the title compound **2.5** (860 mg, 2.31 mmol, 91%) as a white solid: mp 47–49 °C (hexanes– Et_2O); lit. mp 46–48 °C.⁴⁵

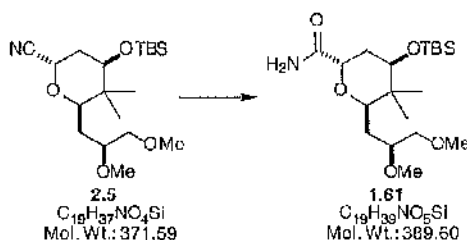
(2*S*,4*R*,6*R*)-4-(*tert*-Butyldimethylsilyloxy)-2-cyano-6-[(2*R*)-2,3-dimethoxypropyl]-tetrahydro-5,5-dimethyl-2*H*-pyran (5.7b)



By the same procedure described above, diol **5.6b** (390 mg, 1.13 mmol), MeI (0.35 ml, 5.6 mmol) gave the dimethyl ether **5.7b** (341 mg, 0.91 mmol, 81%) as a white solid: mp 72–74 °C (hexanes– Et_2O); $[\alpha]_D^{21} +51.0$ (c 1.0, CHCl_3); ν_{max} $\text{KBr}/\text{cm}^{-1}$ 2953, 2931, 1857, 1473, 1252, 1104, 881, 839; δ_{H} (360 MHz, CDCl_3): 4.86 (1H, dd, J 6.1, 1.0, C11H), 3.73 (1H, dd, J 1.4, 10.0, C15H), 3.70 (1H, dd, J 11.6, 4.7, C13H), 3.48–3.37 (3H, m, C17H , C18H_2), 3.48 (3H, s, OMe), 3.38 (3H, s, OMe), 1.99 (1H, ddd, J 13.5, 11.6, 6.1, $\text{C12H}_A\text{H}_B$), 1.78 (1H, ddd, J 13.6, 4.7, 1.3, $\text{C12H}_A\text{H}_B$), 1.67 (1H, ddd, J 14.4, 9.3, 1.4, $\text{C16H}_A\text{H}_B$), 1.49 (1H, ddd, J 14.5, 10.3, 2.2, $\text{C16H}_A\text{H}_B$), 0.91 (3H, s, C14Me), 0.90 (9H, s, ^tBu), 0.83 (3H, s, C14Me), 0.09 (3H, s, SiMe), 0.07 (3H, s, SiMe); δ_{C} (90 MHz, CDCl_3): 117.8 (0, C10), 78.1 (1, C15), 76.4 (1, C17), 74.3 (2, C18), 72.4 (1, C13), 63.7 (1, C11), 59.3 (1, OMe), 58.5 (1, OMe), 39.4 (0, C14), 33.6 (2, C12), 32.2 (2, C16), 25.7 (3, 3C , $^t\text{BuSi}$), 22.5 (3, C14Me), 17.9 (0, CSi), 12.3 (3, C14Me), –4.2 (3, Me-Si), –5.0 (3, MeSi); m/z (CI, isobutane) 372 $[(\text{M}+\text{H})^+]$, 100%, 340 (5), 314 (5), 287 (5), 240 (5), 213 (20). Found: $(\text{M}+\text{H})^+$, 372.2573 $\text{C}_{19}\text{H}_{38}\text{O}_4\text{NSi}$ requires M , 372.2570. Found: C, 61.56; H, 10.02; N, 3.72%. $\text{C}_{19}\text{H}_{37}\text{NO}_4\text{Si}$ requires C, 61.41; H, 10.04; N, 3.77.

Pedamide :

(2*S*,4*R*)-4-*tert*-Butyldimethylsilyloxy-6-[(*S*)-2,3-dimethoxypropyl]-tetrahydro-5,5-dimethyl-2*H*-pyran-2-carboxamide (1.61).

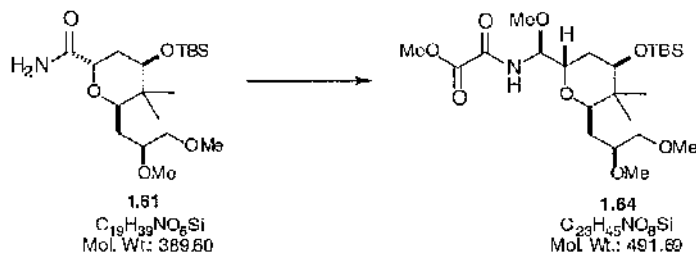


To a solution of nitrile **2.5** (800 mg, 2.15 mmol) in EtOH (18 ml), was added a solution of K_2CO_3 (6 g, 43.4 mmol) in water (12 ml) followed by H_2O_2 (8 ml, 30 % aqueous solution, 52 mmol). The reaction mixture was stirred at room temperature for 5 h and a further portion of H_2O_2 (8 ml, 30 % aqueous solution, 71 mmol) was added. The reaction mixture was stirred for an additional 15 h; before saturated aqueous $\text{Na}_2\text{S}_2\text{O}_3$ (15 ml) was added dropwise until effervescence ceased. The solvent was evaporated and the residue extracted with CH_2Cl_2 (3 x 40 ml). The combined organic extracts were dried, concentrated, and

purified by chromatography on silica gel (40 g) eluting with hexanes/AcOEt (7:3) to give amide **1.61** (728 mg, 1.87 mmol, 87%).

^1H NMR and ^{13}C NMR data in agreement with the literature³²

Methyl 13-*O*-(*tert*-Butyldimethylsilyl)meropederate (**1.64**)



Methyl (2*S*,4*R*)-4-*tert*-Butyldimethylsilyloxy-6-[(*S*)-2,3-dimethoxypropyl]-tetrahydro-5,5-dimethyl-2*H*-pyran-2-carboxamidate (**1.61**)

To a solution of pedamide **1.61** (100 mg, 0.26 mmol) in CH_2Cl_2 (5.5 ml) was added in one portion Me_3OBF_4 (120 mg, 0.84 mmol). After 3 h at room temperature the mixture was poured onto saturated aqueous NaHCO_3 (5 ml) and extracted with CH_2Cl_2 (3 x 5 ml), dried (MgSO_4) and concentrated *in vacuo* to give **5.12** as a foam which was used immediately in the following step.

Methyl (2*S*,4*R*)-4-*tert*-Butyldimethylsilyloxy-6-[(*S*)-2,3-dimethoxypropyl]-tetrahydro-*N*-methoxalyl-5,5-dimethyl-2*H*-pyran-2-carboxamidate (**1.62**)

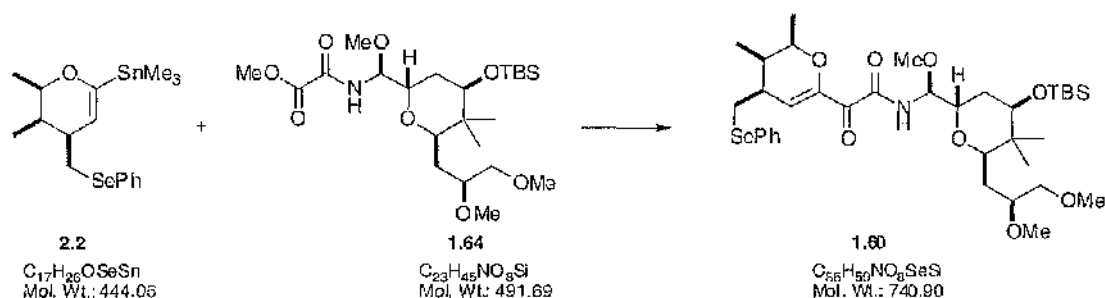
To a solution of crude methyl imidate **5.12** in CH_2Cl_2 (5.5 ml) at -50°C was added pyridine (50 μl , 0.618 mmol, 2.3 eq) followed immediately by methyl oxalyl chloride (32 μl , 0.34 mmol). After 10 min at -50°C the mixture was poured into saturated aqueous NaHCO_3 (10 ml) and extracted with CH_2Cl_2 (3 x 10 ml), dried (MgSO_4) and concentrated *in vacuo* to give **1.62** as a colourless oil which was used immediately in the next step.

Methyl 13-*O*-(*tert*-Butyldimethylsilyl)meropederate (**1.64**)

To a solution of crude *N*-acylimidate **1.62** in toluene (4 ml) at room temperature was added $\text{RhCl}[\text{Ph}_3\text{P}]_3$ (12 mg, 10 μmol). The mixture was cooled to -70°C and freshly prepared catecholborane¹³⁵ (0.80 ml, 0.4 mmol, 0.51 M solution in THF) was added. The reaction mixture was stirred at -70°C for 20 h and poured into saturated aqueous NaHCO_3 (50 ml) and extracted with CH_2Cl_2 (3 x 10 ml). The combined organic extracts were dried (MgSO_4), and concentrated *in vacuo* to give a yellow oil which was purified by column chromatography on silica gel (20 ml) eluting with hexanes/ethyl acetate (9:1 \rightarrow 7:3) to give **1.64** (81 mg, 0.165 mmol, 63.5%).

^1H NMR and ^{13}C NMR data in agreement with the literature³²

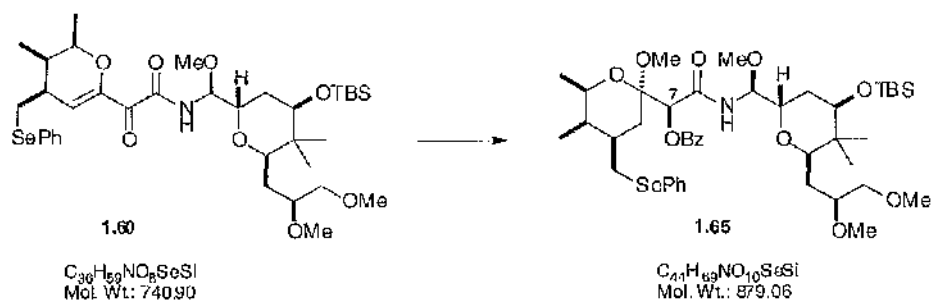
Acylation of lithiated dihydropyran (1.64); Acyldihydropyran (1.60).



To a solution of dihydropyran **2.2** (100 mg, 0.225 mmol) in THF (1.5 ml) at $-80^{\circ}C$ was added BuLi (464 μ l, 0.487 M solution in hexane, 0.226 mmol) and the solution stirred at $-80^{\circ}C$ for 15 min. TMEDA (34 μ l, 0.224 mmol) was added and after 10 min at $-80^{\circ}C$, a solution of ester **1.64** (40 mg, 0.081 mmol) in THF (2.2 ml) was added. After a further 45 min maintaining the temperature below $-60^{\circ}C$, the mixture was treated with saturated aqueous NH_4Cl (2 ml), and extracted with Et_2O (2 x 4 ml). The combined extracts were dried and concentrated to give a yellow oil which was purified by chromatography on silica gel (10 ml), eluting with hexanes/ $EtOAc$ [10:1, 5:1, 3:1] to give coupling product **1.60** (28 mg, 0.038 mmol, 47% based on the right half fragment) as a colorless oil.

1H NMR data in agreement with the literature³²

Reduction of adduct (1.60), addition methanol, benzylation : synthesis of benzoate (1.65).



reduction

To a solution of acyldihydropyran **1.60** (21.4 mg, 0.029 mmol) in THF (1.5 ml) at $-80^{\circ}C$ was added $LiBH(s-Bu)_3$ (0.032 ml, 1.0 M solution in THF, 0.032 mmol). After 10 min at $-80^{\circ}C$ the mixture was treated with brine (0.7 ml) and extracted with CH_2Cl_2 (2 x 4 ml). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was dried by azeotropic distillation with toluene *in vacuo* (2 x 3 ml) to give the corresponding sensitive allylic alcohols.

addition of methanol

The alcohols were immediately dissolved in CH_2Cl_2 (1.3 ml) and MeOH (0.13 ml). Camphorsulfonic acid (2.0 mg, 0.0086 mmol) was added and the solution stirred at room temperature for 3 h. Solid K_2CO_3 (16 mg, 0.11 mmol) was added slowly during 30 min after which the mixture was poured into saturated aqueous $NaHCO_3$ (1 ml) and extracted with CH_2Cl_2 (3 x 5 ml). The combined organic extracts were dried ($MgSO_4$)

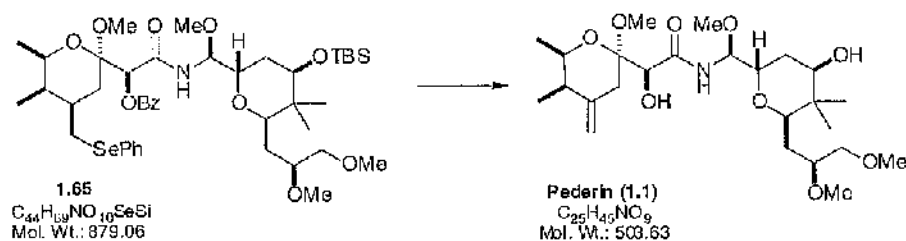
and concentrated *in vacuo*, to give the corresponding diastereoisomeric acetals as a colourless oil which were used immediately in the next step.

benzoylation

Benzoyl chloride (8.2 mg, 6.7 μ l, 0.058 mmol) was added to a stirred solution of acetal alcohols, Et₃N (12 μ l, 0.058 mmol) and DMAP (5.7 mg, 0.046 mmol) in CH₂Cl₂ (1.6 ml) and the reaction mixture was stirred for 15 h at room temperature. MeOH (0.3 ml) was added and after 15 min the mixture was poured into brine (2 ml) and extracted with CH₂Cl₂ (3 x 5 ml). The combined organic extracts were dried (MgSO₄) and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (5 g) eluting with hexanes/EtOAc (10-20%) to give 12.8 mg (0.015 mmol, 50% over 3 steps) of a mixture of the two diastereoisomers at C7 in the ratio 3:1. The mixture was purified by preparative thin layer chromatography eluting with hexanes/ether (1:1) to give pure diastereoisomer **1.65** (5.5 mg, 6.25 μ mol, 22%) along with a mixture of **1.65** and its C7-epimer (6.1 mg, 6.95 μ mol, 24%).

¹H NMR data in agreement with the literature³²

Pederin (1.1)



7-O-Benzoyl-13-O-(tert-butyldimethylsilyl)pederin

Sodium periodate (2.2 mg, 10 μ mol) was added in one portion to a solution of the diastereoisomerically pure selenide **1.65** (5.5 mg, 6.26 μ mol) in MeOH/H₂O (3:1, 1.4 ml). After 30 min the mixture was diluted with Et₂O (5 ml) and washed with H₂O (2 x 5 ml), dried (Na₂SO₄) and concentrated *in vacuo* to give the selenoxide as a colourless oil which was dissolved in toluene (2 ml) whereupon Et₃N (0.95 ml, 6.65 μ mol) was added. After refluxing for 2 min, the reaction mixture was poured into saturated aqueous NaHCO₃ (5 ml) and extracted with Et₂O (2 x 10 ml). The organic extracts were dried (Na₂SO₄) and concentrated *in vacuo* to give a pale yellow oil which was used immediately in the next step.

13-O-(tert-Butyldimethylsilyl)pederin

To the residue in MeOH (1.5 ml) was added aqueous LiOH (0.15 ml, 1.0 M, 0.15 mmol). After 30 min at room temperature the mixture was concentrated, the residue was dissolved in Et₂O (5 ml), washed with H₂O (2 x 1 ml) and brine (1 ml), dried (Na₂SO₄), and concentrated *in vacuo* to give the 13-O-TBS pederin as an oil which was used immediately in the next step.

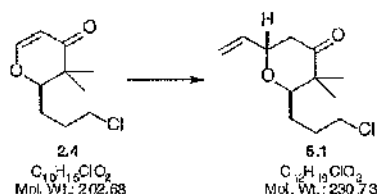
Pederin (1.1)

To a solution of 13-O-TBS pederin in THF (0.4 ml) was added 4 Å molecular sieves (100 mg, crushed and activated *in vacuo* at 180°C) and TBAF (4 mg, 15.3 μ mol). After 24 h at room temperature the reaction mixture was diluted with Et₂O (5 ml) and washed with saturated aqueous NaHCO₃ (1 ml). The aqueous phase was extracted with CH₂Cl₂ (2 x 5 ml) and the combined organic layers dried (Na₂SO₄) and concentrated *in vacuo* to give an oil which was purified by column chromatography on silica gel (1 g) eluting with hexane/AcOEt (7:3) and then with AcOEt to give pederin **1.1** (1.8 mg, 3.57 μ mol, 57% over 4 steps).

δ_{H} (400 MHz, C_6D_6): 7.22 (1H, d, J 10.1, N-H), 5.54 (1H, dd, J 7.9, 10.1, C10-H), 4.74 (1H, t, J = 2.0, C4=CH_a), 4.70 (1H, t, J = 2.0, C4=CH_b), 4.37 (1H, d, J = 2.9, C7-H), 4.14 (1H, d, J = 2.9, C7-OH), 3.86 (1H, dq, J = 2.8, 6.6, C2-H), 3.82-3.77 (1H, m, C11-H), 3.62-3.56 (1H, m, C17-H), 3.50 (1H, dd, J = 3.1, 10.5, C18-H_a), 3.44 (1H, dd, J = 5.9, 10.4, C18-H_b), 3.35-3.31 (2H, m, C15-H and C13-H), 3.32 (3H, s, OMe), 3.27 (3H, s, OMe), 3.20 (3H, s, OMe), 3.15 (3H, s, OMe), 2.70 (1H, d, J = 14.2, C5-H_{eq}), 2.56 (1H, dt, J = 2.0, 14.2, C5-H_{ax}), 1.97 (1H, ddd, J = 2.7, 4.5, 13.4, C12-H_a), 1.90 (1H, dt, J = 2.7, 7.0, C3-H), 1.82 (1H, ddd, 3.1, 10.4, 14.1, C16-H_a), 1.69-1.63 (1H, m, C16-H_b), 1.63-1.58 (1H, m, C12-H_b), 1.55 (1H, d, J = 6.1, C13-OH), 0.94 (3H, d, J = 7.9, C2-Me), 0.89 (3H, d, J = 6.6, C3-Me), 0.784 (3H, s, C14-Me), 0.776 (3H, s, C14-Me); δ_{C} (100 MHz, C_6D_6): 170.8 (0, C8), 145.2 (0, C4), 109.1 (2, C6), 99.0 (0, C6), 78.4 (1, C10), 77.0 (1, C17), 74.9 (1, C15), 73.5 (2, C18), 72.4 (1, C7), 71.7 (1, C11), 70.4 (1, C13), 68.1 (1, C2), 57.6 (3, OMe), 55.7 (3, OMe), 54.8 (3, OMe), 47.6 (3, C6-OMe), 40.4 (1, C3), 37.3 (0, C14), 33.3 (2, C5), 29.8 (2, C16), 28.9 (2, C12), 21.9 (3, C14-Me), 16.5 (3, C2-Me), 12.0 (3, C14-Me), 10.9 (C3-Me).

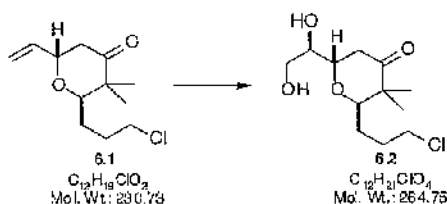
10.5 Synthesis of Mycalamide B (1.5) and 17-epi-Mycalamide B (17-epi-1.5)

(2*R*,6*S*)-2-(3-Chloropropyl)-3,3-dimethyl-6-vinyl-tetrahydro-pyran-4-one (6.1)



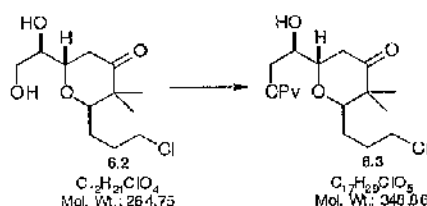
To a stirred solution of enone **2.4** (17.6 g, 86.8 mmol) and copper(I) iodide (1.0 g, 5.35 mmol) in THF (170 ml) at -95°C was added a solution of vinyl magnesium chloride (1.7 M in THF, 90 ml, 153 mmol) over 30 min. The reaction mixture was stirred for 1.5 h at -90°C and then allowed to warm up to -30°C over 1.5 h. Saturated aqueous NH_4Cl (300 ml) was added followed by concentrated ammonia solution (60 ml). The resulting mixture was stirred for 30 min at rt before being extracted with Et_2O (3 x 80 ml). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by Kugelrohr distillation to give vinyl ketone **6.1** (16.0 g, 63.3 mmol, 80%) as a colourless oil: bp $160\text{--}180^\circ\text{C}$ (bath) at 0.07 mm Hg. The diastereoisomeric ratio was 95:5 according to integration of the ^1H NMR spectrum signals (400 MHz, CDCl_3) at δ 2.85 and 2.81 ppm (minor) and 2.67 and 2.55 ppm (major) corresponding to C12H₂. The following data was recorded on the mixture: $[\alpha]_{\text{D}}^{20} +46.5$ (c 1.1, CHCl_3); ν_{max} film/ cm^{-1} 1712, 1128; δ_{H} (400 MHz, CDCl_3): 5.85 (1H, ddd, J 17.2, 10.8, 4.8, C10H), 5.26 (1H, dt, J 7.8, 1.2, C9H_AH_B), 5.3 (1H, dt, J 17.2, 1.2, C9H_AH_B), 4.56 (1H, dt, J 6.0, 4.8, 1.4, C11H), 3.61 (1H, dd, J 10.0, 3.6, C15H), 3.55 (2H, t, J 6.4, C18H₂), 2.67 (1H, dd, J 14.4, 5.9, C12H_AH_B), 2.55 (1H, dd, J 14.4, 5.9, C12H_AH_B), 2.02–1.92 (1H, m, C17H_AH_B), 1.81–1.70 (1H, m, C17H_AH_B), 1.70–1.50 (2H, m, C16H₂), 1.11 (3H, s, C14Me), 1.06 (3H, s, C14Me); δ_{C} (100 MHz, CDCl_3): 211.5 (0, C13), 137.3 (1, C10), 117.9 (2, C9), 79.3 (1, C15), 72.6 (1, C11), 49.8 (0, C14), 45.0 (2, C18), 41.5 (2, C12), 29.3 (2, C17), 25.9 (2, C16), 22.0 (3, C14Me), 19.4 (3, C14Me); m/z (CI) 248 [($\text{M}+\text{NH}_4$)⁺, 100%]; Found: ($\text{M}+\text{H}$)⁺, 230.1071. $\text{C}_{12}\text{H}_{19}\text{ClO}_2$ requires M , 230.1074; Found: C, 62.48; H, 8.18%. $\text{C}_{12}\text{H}_{19}\text{ClO}_2$ requires C, 62.47; H, 8.24.

(2*S*,6*R*)-6-(3-Chloropropyl)-2-[(*R*)-1,2-dihydroxyethyl]-tetrahydro-5,5-dimethyl-2*H*-pyran-4-one (6.2)



The procedure of Sharpless et al. was used.¹⁰⁴ Olefin **6.1** (10.0 g, 43.5 mmol) and hydroquinine 9-phenanthryl ether (Aldrich, 439 mg, 0.9 mmol) were stirred in *t*-BuOH (260 ml) until the ligand dissolved completely. After cooling to rt, water (260 ml), $K_3Fe(CN)_6$ (43.3 g, 131.3 mmol) and K_2CO_3 (18.3 g, 132.6 mmol) were added and the mixture was cooled to 0 °C before addition of potassium osmate dihydrate (267 mg, 0.72 mmol). The reaction mixture was stirred for 3 h at 0 °C, then treated with saturated aqueous Na_2SO_3 (400 ml) and water (100 ml). After stirring at ambient temperature for 30 min the mixture was extracted with CH_2Cl_2 (400 ml + 2 x 200 ml). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo* to give the crude diol. Filtration through silica gel (100 g, 10–40% EtOAc in Et₂O) afforded diol **6.2** (8.63 g, 32.7 mmol, 75%) as a 13:1 mixture of diastereoisomers according to integration of ¹H NMR signals (360 MHz, $CDCl_3$) derived from the *gem*-dimethyl groups [δ 1.26 ppm (major) and 1.28 ppm (minor)] : $[\alpha]_D^{19}$ –8.0 (*c* 1.1, $CHCl_3$); ν_{max} film/ cm^{-1} 3412, 1712; δ_H (400 MHz, $CDCl_3$): 3.94 (1H, dt, *J* 9.7, 4.6, C11-H), 3.81 (1H, ddd, *J* 9.8, 6.2, 3.7, C10H), 3.77 (1H, dd, *J* 11.9, 3.5, C15H), 3.73 (1H, dd, *J* 11.4, 3.6, C9H_AH_B), 3.65 (1H, dd, *J* 11.3, 6.4, C9H_AH_B), 3.58 (2H, t, *J* 6.0, C18H₂), 2.80 (1H, dd, *J* 14.6, 9.7, C12H_AH_B), 2.38 (1H, dd, *J* 14.6, 4.3, C12H_AH_B), 2.00–1.74 (2H, br, OH), 2.00–1.89 (1H, m, C17H_AH_B), 1.83–1.74 (1H, m, C17H_AH_B), 1.73–1.63 (1H, m, C16H_AH_B), 1.61–1.50 (1H, m, C16H_AH_B), 1.27 (3H, s, C14Me), 1.01 (3H, s, C14Me); δ_C (100 MHz, $CDCl_3$): 212.9 (0, C13), 81.6 (1, C15), 73.6 (1, C10), 71.7 (1, C11), 63.2 (2, C9), 49.6 (0, C14), 44.5 (2, C18), 38.8 (2, C12), 28.7 (2, C17), 25.3 (2, C16), 24.2 (3, C14Me), 19.3 (3, C14Me); *m/z* (CI) 248 [(M+NH₄)⁺, 100%]; Found: C, 54.50; H, 7.74; Cl, 13.72%. C₁₂H₂₁ClO₄ requires C, 54.44; H, 7.94; Cl, 13.42.

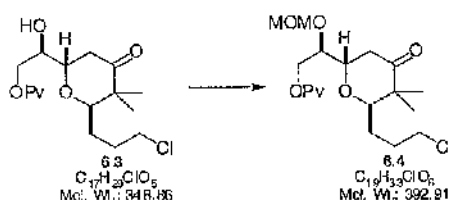
(2*S*,6*R*)-2-[(*R*)-2-(*tert*-Butylcarbonyloxy)-1-hydroxyethyl]-6-(3-chloropropyl)-tetrahydro-5,5-dimethyl-2*H*-pyran-4-one (6.3)



To a solution of diols **6.2** (dr 13:1, 4.8 g, 18.2 mmol) and pyridine (4.45 ml, 55.0 mmol) in CH_2Cl_2 (35 ml) at 0 °C was added pivaloyl chloride (4.6 ml, 37.5 mmol). The reaction mixture was stirred at 0 °C for 1 h, treated with saturated aqueous $NaHCO_3$ and extracted with Et₂O (3 x 70 ml). The combined extracts were washed with aqueous HCl (2M, 50 ml), brine (70 ml), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was filtered through a pad of silica (50 g, 20–50% Et₂O in hexanes) and concentrated *in vacuo*. Diastereoisomerically pure monopivalate ester **6.3** (11.6 g, 33.5 mmol, 78%) was obtained as colourless needles by recrystallisation from hexanes–Et₂O: mp 69–70 °C; $[\alpha]_D^{19}$ –2.0 (*c* 1.0, $CHCl_3$); ν_{max} CCl_4/cm^{-1} 3599, 1716; δ_H (400 MHz, $CDCl_3$) 4.27 (1H, dd, *J* 11.6, 3.6, C9H_AH_B), 4.12 (1H, dd, *J* 11.6, 6.4, C9H_AH_B), 3.96 (1H, dddd, *J* 14.8, 6.4, 5.6, 4.0, C10H), 3.92 (1H, dt, *J* 9.8, 5.3, C11H), 3.80 (1H, dd, *J*

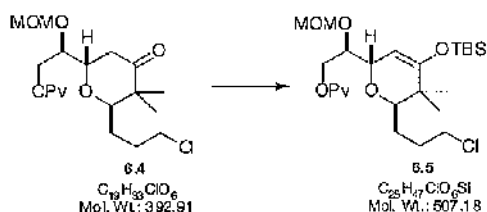
12.0, 3.2, C15H), 3.58 (1H, ddd, J 10.9, 6.2, 1.1, C18H_AH_B), 3.55 (1H, ddd, J 10.9, 6.6, 1.6, C18H_AH_B), 2.82 (1H, dd, J 14.8, 9.6, C12H_AH_B), 2.70–2.20 (1H, d, J 4.4, OH), 2.42 (1H, dd, J 14.8, 4.0, C12H_AH_B), 2.00–1.85 (1H, m, C17H_AH_B), 1.83–1.73 (1H, m, C17H_AH_B), 1.73–1.61 (1H, m, C16H_AH_B), 1.60–1.50 (1H, m, C16H_AH_B), 1.29 (3H, s, C14Me), 1.22 (9H, s, ^tBu), 1.03 (3H, s, C14Me); δ_C (100 MHz, CDCl₃): 211.9 (0, C13), 179.1 (0, ester C=O), 82.1 (1, C15), 72.3 (1, C10), 71.2 (1, C11), 64.9 (2, C9), 49.7 (0, C14), 44.8 (2, C18), 39.1 (0, CMe₃), 38.6 (2, C12), 28.8 (2, C17), 27.4 (3, 3C, CMe₃), 25.4 (2, C16), 24.8 (3, C14Me), 19.5 (3, C14Me); m/z (CI) 349 [(M+H)⁺, 20%]; Found: C, 58.71; H, 8.02; Cl, 10.37%. C₁₇H₂₉ClO₅ requires C, 58.54; H, 8.32; Cl, 10.19.

(2*S*,6*R*)-2-[(*R*)-2-(*tert*-Butylcarbonyloxy)-1-(methoxymethoxy)ethyl]-6-(3-chloropropyl)-tetrahydro-5,5-dimethyl-2*H*-pyran-4-one (6.4)



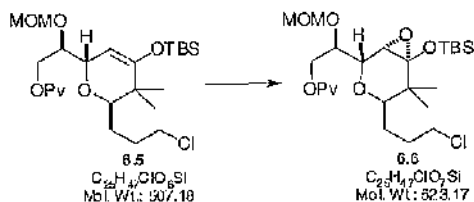
A mixture of alcohol **6.3** (7.1 g, 20.0 mmol), *N*-ethyl-diisopropylamine (10.8 ml, 62.0 mmol), tetrabutylammonium iodide (355 mg, 0.92 mmol), chloromethyl methyl ether (4.7 ml, 62.0 mmol) and anhydrous toluene (55 ml) were stirred at 90 °C for 2 h. The reaction mixture was cooled to rt and treated with saturated aqueous NaHCO₃ (30 ml). The layers were separated and the aqueous layer was extracted with Et₂O (2 x 30 ml). The combined organic extracts were washed with brine (30 ml), dried (Na₂SO₄) and concentrated *in vacuo*. The residue was purified by column chromatography (SiO₂ 50g, 10–40% Et₂O in hexanes) to give the desired MOM ether **6.4** (2.63 g, 6.7 mmol, 97%) as a white solid : mp 42–43 °C (hexanes–Et₂O); $[\alpha]_D^{21} +3.4$ (c 1.4, CHCl₃); ν_{\max} CCl₄/cm⁻¹ 1732, 1716, 1154; δ_H (400 MHz, CDCl₃): 4.69 (1H, d, J 6.9, OCH_AH_BO), 4.61 (1H, d, J 6.9, OCH_AH_BO), 4.29 (1H, dd, J 11.8, 4.3, C9H_AH_B), 3.99 (1H, dd, J 11.8, 4.9, C9H_AH_B), 3.92 (1H, dt, J 9.9, 4.6, C11H), 3.78 (1H, q, J 5.0, C10H), 3.68 (1H, dd, J 11.7, 3.2, C15H), 3.47 (2H, t, J 5.5, C18H₂), 3.30 (3H, s, OMe), 2.71 (1H, dd, J 14.8, 10.0, C12H_AH_B), 2.34 (1H, dd, J 14.7, 4.3, C12H_AH_B), 1.90–1.80 (1H, m, C17H_AH_B), 1.74–1.62 (1H, m, C17H_AH_B), 1.62–1.51 (1H, m, C16H_AH_B), 1.50–1.40 (1H, m, C16H_AH_B), 1.19 (3H, s, C14Me), 1.11 (9H, s, ^tBu), 0.93 (3H, s, C14Me); δ_C (100 MHz, CDCl₃): 211.3 (0, C13), 177.8 (0, ester C=O), 96.2 (2, O–CH₂–O), 81.5 (1, C15), 76.5 (1, C10), 70.3 (1, C11), 62.4 (2, C9), 55.8 (3, OMe), 49.3 (0, C14), 44.4 (2, C18), 38.7 (2, C12), 38.6 (0, CMe₃), 28.4 (2, C17), 26.9 (3, 3C, CMe₃), 24.9 (2, C16), 24.3 (3, C14Me), 19.1 (3, C14Me); m/z (CI) 393 [(M+H)⁺, 7%]; Found: C, 58.36; H, 8.12; Cl, 8.94%. C₁₉H₃₃ClO₆ requires C, 58.09; H, 8.41; Cl, 9.04.

(2*S*,6*R*)-2-[(*R*)-2-(*tert*-Butylcarbonyloxy)-1-(methoxymethoxy)ethyl]-4-[(*tert*-butyldimethylsilyl)oxy]-6-(3-chloropropyl)-5,6-dihydro-5,5-dimethyl-2*H*-pyran (6.5)



To a mixture of ketone **6.4** (17.5 g, 44.5 mmol) and triethylamine (12.1 ml, 86.6 mmol) in CH_2Cl_2 (70 ml) at 0 °C was added TBSOTf (12.1 ml, 51.5 mmol) in a dropwise fashion over 5 min. After the addition was complete the cooling bath was removed and the reaction mixture stirred for 1.5 h at rt. Saturated aqueous NaHCO_3 (200 ml) was added and the mixture extracted with hexanes (3 x 50 ml). The combined extracts were dried (Na_2SO_4) and concentrated *in vacuo* to give crude silyl enol ether **6.5**. TBSOH was removed under vacuum at 50 °C, 1 mm/Hg overnight to give the desired silyl enol ether **6.5** (19.2 g, 37.8 mmol, 85%) as a clear colourless oil: $[\alpha]_D^{17} +10.3$ (c 1.1, CHCl_3); ν_{max} film/ cm^{-1} 1732, 1664, 1154; δ_{H} (400 MHz, CDCl_3): 4.74 (1H, d, *J* 3.0, C12H), 4.72 (1H, d, *J* 6.8, $\text{OCH}_A\text{H}_B\text{O}$), 4.66 (1H, d, *J* 6.8, $\text{OCH}_A\text{H}_B\text{O}$), 4.46 (1H, dd, *J* 11.9, 2.5, C9 H_AH_B), 4.20 (1H, dd, *J* 7.8, 3.0, C11H), 4.08 (1H, dd, *J* 12.0, 5.7, C9 H_AH_B), 3.71 (1H, ddd, *J* 7.9, 5.7, 2.5, C10H), 3.65–3.53 (2H, m, C18 H_2), 3.40 (1H, dd, *J* 10.6, 2.1, C15H), 3.37 (3H, s, OMe), 2.10–2.00 (1H, m, C17 H_AH_B), 1.83–1.70 (1H, m, C17 H_AH_B), 1.70–1.59 (1H, m, C16 H_AH_B), 1.59–1.49 (1H, m, C16 H_AH_B), 1.19 (9H, s, tBu), 1.01 (3H, s, C14Me), 0.93 (3H, s, C14Me), 0.92 (9H, s, tBuSi), 0.16 (3H, s, MeSi), 0.15 (3H, s, MeSi); δ_{C} (100 MHz, CDCl_3): 178.2 (0, ester C=O), 156.0 (0, C13), 98.2 (1, C12), 96.4 (2, OCH_2O), 79.0 (1, C15), 77.3 (1, C10), 70.0 (1, C11), 64.2 (2, C9), 55.8 (3, OMe), 45.2 (2, C18), 38.7 (0, CMe₃ or C14), 38.4 (0, C14 or CMe₃), 29.6 (2, C17), 27.1 (3, 3C, tBuC=O), 26.2 (2, C16), 25.6 (3, 3C, tBuSi), 23.0 (3, C14Me), 19.7 (3, C14Me), 18.1 (0, CSi), –4.5 (3, MeSi), –4.8 (3, MeSi); *m/z* (Cl, NH_3) 524 [(M+ NH_4)⁺, 40%]; Found: (M+H)⁺, 507.2910. $\text{C}_{25}\text{H}_{48}\text{ClO}_6\text{Si}$ requires *M*, 507.2909; Found: C, 59.31; H, 9.01%. $\text{C}_{25}\text{H}_{47}\text{ClO}_6\text{Si}$ requires C, 59.35; H, 9.23.

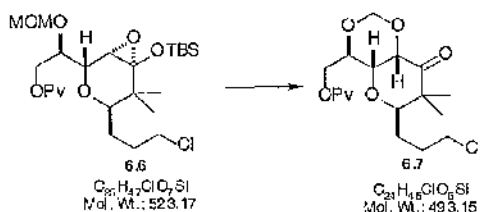
(2*R*,3*S*,4*S*,6*R*)-2-[(*R*)-2-(*tert*-Butylcarbonyloxy)-1-(methoxymethoxy)ethyl]-4-[(*tert*-butyldimethylsilyl)oxy]-6-(3-chloropropyl)-3,4-epoxy-tetrahydro-5,5-dimethyl-2*H*-pyran (6.6)



A solution of *m*-chloroperbenzoic acid (15.2 g, 57–80%) in CH_2Cl_2 (150 ml) was dried over Na_2SO_4 , filtered and stirred with sodium hydrogen orthophosphate (11.2 g, 78.7 mmol) at rt for 30 min. The mixture was then cooled to 0 °C and a solution of enol ether **6.5** (8.58 g, 17.0 mmol) in CH_2Cl_2 (56 ml) was added dropwise over 20 min. The reaction mixture was stirred for 40 min, treated with saturated aqueous Na_2SO_3 and hexanes (500 ml). The phases were separated and the organic layer was extracted with aqueous NaOH (2*M*, 2 x 70 ml), washed with water (70 ml), brine (70 ml), dried (Na_2SO_4) and concentrated *in vacuo* to afford crude oxirane **6.6** (9.58 g, 18.4 mmol, ca. 100%, single diastereoisomer) as a clear colourless oil: $[\alpha]_D^{20} +10.0$ (c 2.0, CHCl_3); ν_{max} film/ cm^{-1} 1732, 1152; δ_{H} (360 MHz, CDCl_3): 4.78 (1H, d, *J* 6.7, $\text{OCH}_A\text{H}_B\text{O}$), 4.74 (1H, d, *J* 6.7, $\text{OCH}_A\text{H}_B\text{O}$), 4.54 (1H, dd, *J* 12.0, 1.8, C9 H_AH_B), 4.05 (1H, dd, *J* 9.9, 3.2,

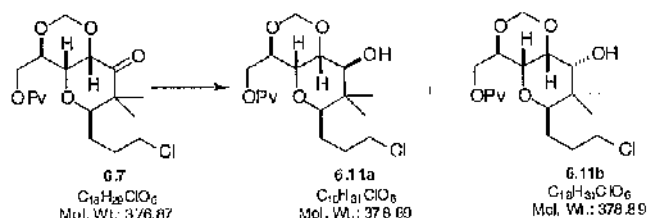
C11H), 4.01 (1H, dd, J 12.0, 4.3, C9H_AH_B), 3.94 (1H, ddd, J 9.9, 4.1, 1.6, C10H), 3.57–3.47 (2H, m, C18H₂), 3.51 (1H, d, J 3.2, C12H), 3.43 (3H, s, OMe), 3.27 (1H, dd, J 10.3, 1.4, C15H), 2.00–1.85 (1H, m), 1.70–1.50 (2H, m), 1.40–1.30 (1H, m), 1.22 (9H, s, ^tBuC=O), 1.05 (3H, s, C14Me), 0.98 (3H, s, C14Me), 0.91 (9H, s, ^tBuSi), 0.14 (3H, s, SiMe), 0.06 (3H, s, SiMe); δ_C (90 MHz, CDCl₃): 178.5 (0), 96.3 (2), 86.6 (0), 76.0 (1), 71.7 (1), 68.9 (1), 63.6 (2), 60.4 (1), 56.2 (3), 45.3 (2), 39.1 (0), 38.9 (0), 30.1 (2), 27.4 (3, 3C), 26.9 (2), 25.8 (3, 3C), 18.7 (3), 18.0 (0), 16.8 (3), –3.1 (3), –3.4 (3); m/z (CI, NH₃) 540 [(M+NH₄)⁺, 100%]; Found: (M+H)⁺, 522.2781. C₂₅H₄₇ClO₇Si requires M , 522.2780.

(1S,5R,6R,8R)-5-(*tert*-Butylcarbonyloxy)methyl-8-(3-chloropropyl)-9,9-dimethyl-2,4,7-trioxabicyclo[4.4.0]decan-10-one (6.7)



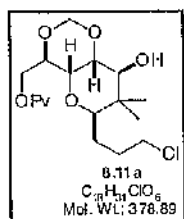
A mixture of crude oxirane **6.6** (3.5 g, *ca.* 92% pure, 6.17 mmol) in CH₂Cl₂ (15 ml) was added *via* cannula to a solution of dimethoxymethane (30 ml) and P₂O₅ (2.5 g, 8.8 mmol) in CH₂Cl₂ (15 ml) at 0 °C over 5 min. The cool bath was removed and the reaction mixture was stirred at rt for 2 h whereupon the reaction mixture was poured onto saturated aqueous NaHCO₃ (50 ml). The phases were separated and the aqueous layer was extracted with CH₂Cl₂ (3 x 100 ml). The combined extracts were washed with brine (100 ml), dried (Na₂SO₄) and concentrated *in vacuo*. A ¹H NMR spectrum of the crude product showed a 15:1 ratio of diastereoisomers by integration of the ¹H NMR signals (360 MHz, CDCl₃) derived from *gem*-dimethyl groups at δ 1.06 ppm (major) and 1.32 ppm (minor). The crude product was purified by column chromatography (SiO₂ 45 g, 10–40% Et₂O in hexanes) to give ketone **6.7** (1.79 g, 4.75 mmol, 77%) as a white solid: mp 88–89 °C (hexanes–Et₂O); [α]_D²⁰ +166.6 (*c* 1.4, CHCl₃); ν_{max} KBr/cm^{–1} 1724, 1282, 1164, 1150; δ_H (400 MHz, CDCl₃): 4.94 (1H, d, J 7.8, C12H), 4.87 (1H, d, J 6.5, OCH_AH_BO), 4.83 (1H, d, J 6.5, OCH_AH_BO), 4.50 (1H, dd, J 12.2, 1.6, C9H_AH_B), 4.30 (1H, dd, J 10.9, 7.8, C11H), 4.03 (1H, dd, J 12.2, 6.9, C9H_AH_B), 3.88 (1H, ddd, J 10.8, 6.9, 1.6, C10H), 3.60 (2H, dt, J 6.8, 5.1, C18H₂), 3.56 (1H, dd, J 12.4, 4.0, C15H), 2.12–2.02 (1H, m, C17H_AH_B), 1.90–1.70 (1H, m, C17H_AH_B), 1.70–1.61 (2H, m, C16H₂), 1.22 (12H, s, ^tBuC=O and C14Me), 1.08 (3H, s, C14Me); δ_C (100 MHz, CDCl₃): 208.2 (0, C13), 178.3 (0, ester C=O), 89.8 (2, OCH₂O), 78.6 (1, C15), 73.3 (1, C12), 72.6 (1, C10), 70.0 (1, C11), 62.8 (2, C9), 51.0 (0, C14 or CMe₃), 45.0 (2, C18), 38.7 (0, CMe₃ or C14), 29.4 (2, C17), 27.0 (3, 3C, ^tBuC=O), 26.7 (2, C16), 19.0 (3, C14Me), 18.9 (3, C14Me); m/z (CI, NH₃) 394 [(M+NH₄)⁺, 100%]. Found: (M+H)⁺, 376.1652. C₁₈H₃₀ClO₆ requires M , 376.1653. Found: C, 57.37; H, 7.64; Cl, 9.46%. C₁₈H₂₉ClO₆ requires C, 57.37; H, 7.70; Cl, 9.43.

Reduction of ketone 6.7



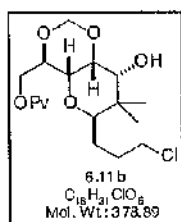
Two procedures were used the most selective being a modified Meerwein–Ponndorf–Verley reduction. Thus, trimethylaluminium (2.5 ml, 2.0 M in hexane, 5 mmol) was added to isopropanol (50 ml). The solution was stirred for 30 min at rt before solid ketone **6.7** (500 mg, 1.325 mmol) was added. The reaction mixture was stirred for 24 h at rt, then concentrated *in vacuo*. The residue was diluted with EtOAc (50 ml) and treated with HCl (0.5M, 25 ml). The phases were separated and the aqueous phase was extracted with EtOAc (2 x 25 ml). The combined organic extracts were dried (MgSO₄) and concentrated *in vacuo* to give a mixture of the ketone **6.7**, the alcohol **6.11a**, and the undesired alcohol **6.11b** as a colourless oil. Separation by column chromatography (SiO₂, 10 g, 30–50% Et₂O in hexanes) gave ketone **6.7** (140 mg, 0.371 mmol, 28%), and a mixture of alcohols **6.7a** and **6.7b** (332 mg, 0.878 mmol, 66%, or 92% based on recovered starting material) in the ratio 6:1 (major product is the desired one). The alcohols were then separated by a second column chromatography (SiO₂, 10 g, 10–50% Et₂O in hexanes) to give alcohols **6.7a** and **6.7b** as colourless oils.

(1*S*,5*R*,6*R*,8*R*,10*S*)-5-(*tert*-Butylcarbonyloxy)methyl-8-(3-chloropropyl)-9,9-dimethyl-2,4,7-trioxabicyclo[4.4.0]decan-10-ol (**6.11a**)



$[\alpha]_D^{20} +87.0$ (c 2.0, CHCl₃); ν_{\max} film/cm⁻¹ 3486, 1740, 1728; δ_H (400 MHz, CDCl₃): 4.94 (1H, d, *J* 6.4, OCH_AH_BO), 4.80 (1H, d, *J* 6.8, OCH_AH_BO), 4.49 (1H, dd, *J* 12.0, 2.0, C9H_AH_B), 4.16 (1H, ddd, *J* 10.4, 6.8, 1.6, C10H), 4.06 (1H, dd, *J* 10.4, 6.4, C11H), 4.03–3.94 (3H, m), 3.65–3.50 (2H, m, C18H₂), 3.26 (1H, dd, *J* 10.4, 1.6, C15H), 2.24 (1H, br, OH), 2.10–1.90 (1H, m), 1.80–1.60 (2H, m), 1.50–1.37 (1H, m), 1.23 (9H, s, ^tBuCOO), 1.04 (3H, s, C14Me), 0.93 (3H, s, C14Me); δ_C (100 MHz, CDCl₃): 178.6 (0), 86.7 (2), 78.1 (1), 72.8 (1), 71.4 (1), 69.4 (1), 67.4 (1), 63.8 (2), 45.4 (2), 40.8 (0), 39.0 (0), 29.7 (2), 27.3 (3, 3C), 26.3 (2), 23.1 (3), 12.6 (3); *m/z* (CI) 379 [(M+H)⁺, 100%]. Found: C, 57.11; H, 8.10%. C₁₈H₃₁ClO₆ requires C, 57.07; H, 8.19.

(1*S*,5*R*,6*R*,8*R*,10*R*)-5-(*tert*-Butylcarbonyloxy)methyl-8-(3-chloropropyl)-9,9-dimethyl-2,4,7-trioxabicyclo[4.4.0]decan-10-ol (**6.11b**)

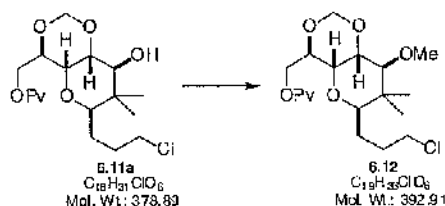


$[\alpha]_D^{22} +66.3$ (c 0.3, CHCl_3); ν_{max} film/ cm^{-1} 3496, 1734; δ_{H} (360 MHz, CDCl_3): 5.15 (1H, d, J 5.8, $\text{OCH}_A\text{H}_B\text{O}$), 4.89 (1H, d, J 5.8, $\text{OCH}_A\text{H}_B\text{O}$), 4.30 (2H, apparent d, J 5.7, C9H_2), 4.21 (1H, dt, J 10.4, 5.2, C10H), 4.06 (1H, t, J 3.8), 3.75–3.62 (3H, m), 3.59 (2H, t, J 5.5, C18H_2), 2.32 (1H, d, J 8.1, OH), 2.00–1.58 (4H, m), 1.21 (9H, s, $^t\text{BuC=O}$), 1.13 (3H, s, C14Me), 0.96 (3H, s, C14Me); δ_{C} (100 MHz, CDCl_3): 178.3 (0), 89.1 (2), 78.0 (1, broad signal), 74.3 (1, broad signal), 73.1 (1), 70.2 (1), 65.4 (1), 62.3 (2), 45.1 (2), 38.9 (0), 38.5 (0), 29.3 (2), 27.2 (3, 3C), 24.0 (2), 22.6 (3), 22.2 (3, broad signal); δ_{C} (90 MHz, CDCl_3 , 333 K): 178.1 (0), 89.1 (2), 78.0 (1), 74.3 (1), 73.1 (1), 70.3 (1), 65.7 (1), 62.6 (2), 44.9 (2), 38.9 (0), 38.4 (0), 29.5 (2), 27.2 (3, 3C), 24.1 (2), 22.7 (3), 22.1 (3); m/z (CI) 379 [($\text{M}+\text{H}$) $^+$, 100%]. Found: C, 57.05; H, 8.05%. $\text{C}_{18}\text{H}_{31}\text{ClO}_6$ requires C, 57.07; H, 8.19.

Alcohols **6.11a** and **6.11b** were also generated by reduction of ketone **6.7** with KBH_4 in the presence of $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$. A solution of ketone **6.7** (1.80 g, 4.8 mmol) and $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ (2.6 g, 7.1 mmol) in anhydrous methanol (90 ml) was stirred at rt for 15 min and then cooled to 0 °C. Solid KBH_4 (740 mg, 14.1 mmol) was added (gas evolution!). After 1.5 h acetone (1 ml) was added to the reaction mixture followed by saturated aqueous NaHCO_3 (50 ml). The methanol was removed *in vacuo* and the aqueous phase extracted with CH_2Cl_2 (3 x 50 ml). The combined extracts were washed with brine (50 ml), dried (Na_2SO_4) and concentrated *in vacuo*. ^1H NMR spectrum of the crude product showed a 1:2 ratio of diastereoisomers by integration of ^1H NMR signals (360 MHz, CDCl_3) derived from the *gem*-dimethyl groups at δ 1.14 ppm (major) and 1.05 ppm (minor). The undesired alcohol **6.11b** was the major product. The crude product was purified by column chromatography (SiO_2 50 g, 30–50% Et_2O in hexanes) to give a mixture of alcohols **6.11a,b** (1.72 g, 4.56 mmol, 95%) as a colourless oil. The diastereoisomers were separated by column chromatography (SiO_2 150 g, hexanes– Et_2O 20–40%)

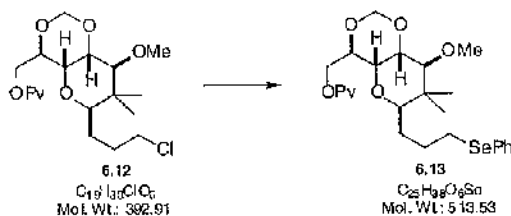
The undesired alcohol **6.11b** was converted back to ketone **6.7** by Dess–Martin oxidation.¹²⁵ Dess–Martin periodinane (2.7 g, 6.35 mmol) was added in one portion to a stirred solution of alcohol **6.11b** (1.6 g, 4.3 mmol) in CH_2Cl_2 (20 ml). The reaction mixture was stirred at rt for 25 min and treated with saturated aqueous $\text{Na}_2\text{S}_2\text{O}_3$ (25 ml) and saturated aqueous NaHCO_3 (20 ml). After 1 h the phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 20 ml). The combined extracts were dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography (SiO_2 10 g, 10–30% Et_2O in hexanes) to give ketone **6.7** (1.61 g, 4.3 mmol, 100%).

(1*R*,5*R*,6*R*,8*R*,10*S*)-5-(*tert*-Butylcarbonyloxy)methyl-8-(3-chloropropyl)-10-methoxy-9,9-dimethyl-2,4,7-trioxabicyclo[4.4.0]decane (6.12)



A solution of alcohol **6.11a** (4.2 g, 11.0 mmol) in THF (25 ml) was added dropwise to a stirred solution of sodium bis(trimethylsilyl)amide (2M in THF, 7.3 ml, 14.5 mmol) in THF (5 ml) at -78°C . After 5 min methyl trifluoromethanesulfonate (2.5 ml, 22.4 mmol) was added dropwise. The reaction mixture was stirred at -78°C for 20 min, treated with saturated aqueous NaHCO_3 (50 ml) and extracted with Et_2O (3 x 50 ml). The combined organic extracts were dried (MgSO_4) and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2 , 5–20% Et_2O in hexanes) to give methyl ether **6.12** (3.7 g, 9.41 mmol, 86%) as a colourless oil: $[\alpha]_{\text{D}}^{21} +54.7$ (*c* 1.1, CHCl_3); ν_{max} film/ cm^{-1} 1732, 1162, 1112, 1040; δ_{H} (400 MHz, CDCl_3): 4.98 (1H, d, *J* 6.6, $\text{OCH}_A\text{H}_B\text{O}$), 4.84 (1H, d, *J* 6.6, $\text{OCH}_A\text{H}_B\text{O}$), 4.48 (1H, dd, *J* 12.0, 1.6, $\text{C9H}_A\text{H}_B$), 4.19–4.13 (2H, m, C10H , C12H), 4.00 (1H, dd, *J* 12.0, 7.0, $\text{C9H}_A\text{H}_B$), 3.92 (1H, dd, *J* 10.6, 6.8, C11H), 3.63–3.50 (2H, m, C18H_2), 3.55 (3H, s, OMe), 3.42 (1H, d, *J* 10.3, C13H), 3.24 (1H, d, *J* 9.7, C15H), 2.02–1.94 (1H, m, $\text{C17H}_A\text{H}_B$), 1.80–1.68 (1H, m, $\text{C17H}_A\text{H}_B$), 1.68–1.60 (1H, m, $\text{C16H}_A\text{H}_B$), 1.46–1.35 (1H, m, $\text{C16H}_A\text{H}_B$), 1.22 (9H, s, tBuC=O), 1.00 (3H, s, C14Me), 0.86 (3H, s, C14Me); δ_{C} (100 MHz, CDCl_3): 178.4 (0, ester C=O), 86.9 (2, OCH_2O), 79.2 (1, C13), 78.0 (1, C15), 73.3 (1, C10 or C12), 71.2 (1, C12 or C10), 67.3 (1, C11), 63.7 (2, C9), 61.7 (3, OMe), 45.2 (2, C18), 41.6 (0, C14), 38.8 (0, CMe_3), 29.5 (2, C17), 27.1 (3, 3C, tBu), 26.1 (2, C16), 23.1 (3, C14Me), 13.4 (3, C14Me); *m/z* (CI) 393 [(*M*+*H*)⁺, 100%]. Found: (*M*+*H*)⁺, 393.2040. $\text{C}_{19}\text{H}_{34}\text{ClO}_6$ requires *M*, 393.2044. Found: C, 58.19; H, 8.41%. $\text{C}_{19}\text{H}_{33}\text{ClO}_6$ requires C, 58.09; H, 8.41%.

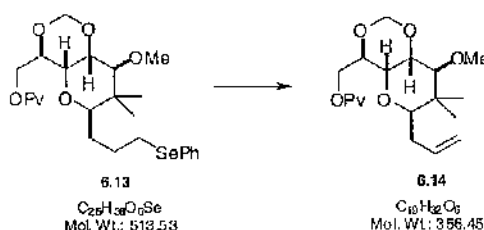
(1*R*,5*R*,6*R*,8*R*,10*S*)-5-(*tert*-Butylcarbonyloxy)methyl-10-methoxy-9,9-dimethyl-8-(3-phenylselenenylpropyl)-2,4,7-trioxabicyclo[4.4.0]decane (6.13)



Solid NaBH_4 (610 mg, 16.1 mmol) was added in several batches to a stirred suspension of diphenyl diselenide (2.5 g, 8.26 mmol) in anhydrous ethanol (30 ml) to cause exothermic reaction. The reaction mixture was stirred at rt until a clear yellow solution was obtained. A solution of chloride **6.12** (4.2 g, 10.7 mmol) in ethanol (30 ml) was then added *via* cannula and the resulting mixture was heated at reflux for 10 min. The reaction mixture was cooled to rt, poured onto saturated aqueous NaHCO_3 (200 ml) and extracted with Et_2O (3 x 200 ml). The combined organic extracts were washed with aqueous NaOH (2M, 100 ml) and brine (100 ml), dried (MgSO_4) and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2 , 10–40% Et_2O in hexanes) to give selenide **6.13** (5.25 g, 10.2 mmol, 96%) as a colourless oil: $[\alpha]_{\text{D}}^{20} +71.3$ (*c* 1.6, CHCl_3); ν_{max} film/ cm^{-1} 1732, 1580, 1186, 1162, 1112, 1040; δ_{H} (400

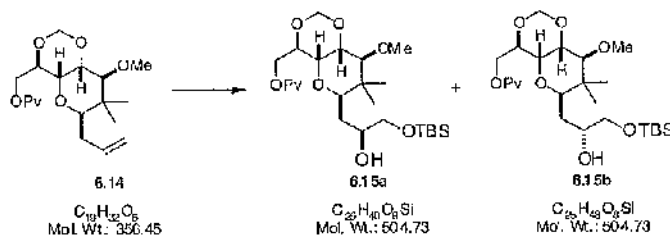
MHz, CDCl_3): 7.54–7.51 (2H, m), 7.31–7.23 (3H, m), 4.99 (1H, d, J 6.6, $\text{OCH}_A\text{H}_B\text{O}$), 4.88 (1H, d, J 6.6, $\text{OCH}_A\text{H}_B\text{O}$), 4.47 (1H, dd, J 12.0, 1.6, $\text{C}9\text{H}_A\text{H}_B$), 4.20–4.16 (1H, m, $\text{C}10\text{H}$ collapsed by $\text{C}12\text{H}$), 4.18 (1H, dd, J 10.3, 6.8, $\text{C}12\text{H}$), 4.02 (1H, dd, J 12.1, 6.9, $\text{C}9\text{H}_A\text{H}_B$), 3.97 (1H, dd, J 10.6, 6.8, $\text{C}11\text{H}$), 3.59 (3H, s, OMe), 3.42 (1H, d, J 10.3, $\text{C}13\text{H}$), 3.23 (1H, dd, J 10.2, 1.4, $\text{C}15\text{H}$), 2.96 (2H, t, J 7.0, $\text{C}18\text{H}_2$), 2.00–1.90 (1H, m, $\text{C}17\text{H}_A\text{H}_B$), 1.75–1.65 (1H, m, $\text{C}17\text{H}_A\text{H}_B$), 1.65–1.57 (1H, m, $\text{C}16\text{H}_A\text{H}_B$), 1.47–1.40 (1H, m, $\text{C}16\text{H}_A\text{H}_B$), 1.25 (9H, s, $^t\text{BuC=O}$), 1.00 (3H, s, $\text{C}14\text{Me}$), 0.87 (3H, s, $\text{C}14\text{Me}$); δ_{C} (100 MHz, CDCl_3): 178.3 (0, ester C=O), 132.7 (1, 2C), 130.3 (0), 129.0 (1, 2C), 126.7 (1), 86.9 (2, OCH_2O), 79.2 (1, $\text{C}13$), 78.1 (1, $\text{C}15$), 73.4 (1, $\text{C}10$ or $\text{C}12$), 71.2 (1, $\text{C}12$ or $\text{C}10$), 67.3 (1, $\text{C}11$), 63.6 (2, $\text{C}9$), 61.7 (3, OMe), 41.6 (0, $\text{C}14$ or CMe_3), 38.9 (0, CMe_3 or $\text{C}14$), 28.6 (2, $\text{C}18$), 27.9 (2, $\text{C}17$ or $\text{C}16$), 27.1 (3, 3C, ^tBu); 27.1 (2, $\text{C}16$ or $\text{C}17$), 23.2 (3, $\text{C}14\text{Me}$), 13.4 (3, $\text{C}14\text{Me}$); m/z (EI) 514 [($\text{M}+\text{H}$) $^{+}$, 33%], 357 (15), 243 (15), 193 (20), 113 (25), 71 (100). Found: ($\text{M}+\text{H}$) $^{+}$, 514.1830. $\text{C}_{25}\text{H}_{38}\text{O}_6\text{Se}$ requires M , 514.1835. Found: C, 58.47; H, 7.48%. $\text{C}_{25}\text{H}_{38}\text{O}_6\text{Se}$ requires C, 58.48; H, 7.41.

(1*R*,5*R*,6*R*,8*R*,10*S*)-5-(*tert*-Butylcarbonyloxy)methyl-10-methoxy-9,9-dimethyl-8-(prop-2-enyl)-2,4,7-trioxabicyclo[4.4.0]decane (6.14)



Sodium metaperiodate (3.5 g, 16.8 mmol) was added in one portion to a stirred mixture of selenide **6.13** (5.20 g, 10.1 mmol), water (60 ml) and MeOH (150 ml) at rt. The reaction mixture was stirred for 25 min then diluted with water (50 ml) and extracted with CH_2Cl_2 (3 x 50 ml). To the combined organic extracts was added 5 ml of triethylamine and the extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was dissolved in toluene (110 ml) and triethylamine (110 ml) and heated at reflux for 10 min. The yellow reaction mixture was allowed to cool to rt, poured onto saturated aqueous NaHCO_3 (200 ml) and extracted with CH_2Cl_2 (3 x 100 ml). The combined organic extracts were dried (Na_2SO_4) and concentrated at rt *in vacuo*. The residue was dissolved in toluene (7 ml) and purified by column chromatography (SiO_2 , hexanes) until the yellow band eluted and then Et_2O :hexanes (5–50%) to give olefin **6.14** (3.55 g, 9.96 mmol, 98%) as a colourless oil: $[\alpha]_{\text{D}}^{22} +25.9$ (c 1.4, CHCl_3); ν_{max} film/ cm^{-1} 1732, 1480, 1284; δ_{H} (400 MHz, CDCl_3): 5.84 (1H, ddt, J 18.0, 11.4, 6.8, $\text{C}17\text{H}$), 5.08 (1H, ddm, J 5.6, 1.2, $\text{C}18\text{H}_A\text{H}_B$), 5.04 (1H, dm, J 1.2, $\text{C}18\text{H}_A\text{H}_B$), 4.99 (1H, d, J 6.6, $\text{OCH}_A\text{H}_B\text{O}$), 4.86 (1H, d, J 6.6, $\text{OCH}_A\text{H}_B\text{O}$), 4.47 (1H, dd, J 12.0, 1.9, $\text{C}9\text{H}_A\text{H}_B$), 4.20–4.15 (1H, m, $\text{C}10\text{H}$ collapsed by $\text{C}12\text{H}$), 4.18 (1H, dd, J 10.2, 6.8, $\text{C}12\text{H}$), 4.06 (1H, dd, J 12.0, 6.6, $\text{C}9\text{H}_A\text{H}_B$), 3.99 (1H, dd, J 10.6, 6.8, $\text{C}11\text{H}$), 3.57 (3H, s, OMe), 3.44 (1H, d, J 10.2, $\text{C}13\text{H}$), 3.30 (1H, dd, J 10.1, 2.3, $\text{C}15\text{H}$), 2.19 (1H, dddt, J 14.4, 10.2, 7.1, 1.2, $\text{C}16\text{H}_A\text{H}_B$), 2.12–2.03 (1H, m, $\text{C}16\text{H}_A\text{H}_B$), 1.23 (9H, s, $^t\text{BuC=O}$), 1.02 (3H, s, $\text{C}14\text{Me}$), 0.89 (3H, s, $\text{C}14\text{Me}$); δ_{C} (100 MHz, CDCl_3): 178.6 (0, ester C=O), 135.8 (1, $\text{C}17$), 116.7 (2, $\text{C}18$), 87.2 (2, OCH_2O), 79.3 (1, $\text{C}13$), 78.5 (1, $\text{C}15$), 73.5 (1, $\text{C}12$), 71.3 (1, $\text{C}10$), 67.3 (1, $\text{C}11$), 63.5 (2, $\text{C}9$), 61.8 (3, OMe), 41.6 (0, $\text{C}14$), 38.9 (0, CMe_3), 33.4 (2, $\text{C}16$), 27.2 (3, 3C, ^tBu), 23.2 (3, $\text{C}14\text{Me}$), 13.4 (3, $\text{C}14\text{Me}$); m/z (CI) 357 [($\text{M}+\text{H}$) $^{+}$, 100%]. Found: ($\text{M}+\text{H}$) $^{+}$, 357.2277. $\text{C}_{19}\text{H}_{32}\text{O}_6$ requires M , 357.2276. Found: C, 64.04; H, 9.19%. $\text{C}_{19}\text{H}_{32}\text{O}_6$ requires C, 64.04; H, 9.00.

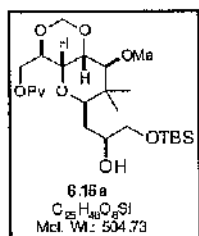
Sharpless asymmetric dihydroxylation of alkene 6.14



Alkene **6.14** (2 g, 5.61 mmol) and dihydroquinine 9-phenanthryl ether¹⁰⁴ (86 mg, 0.170 mmol) were stirred in ^tBuOH (40 ml) until the crystals of ligand dissolved completely. After cooling to rt, water (40 ml), K₃Fe(CN)₆ (5.6 g, 17.1 mmol) and K₂CO₃ (2.3 g, 16.7 mmol) were added and the mixture was cooled to 0 °C. Potassium osmate dihydrate (60 mg, 0.16 mmol) was added and the reaction mixture was stirred for 3 h at 0 °C, then treated with saturated aqueous Na₂SO₃ (70 ml) and extracted with CH₂Cl₂ (3 x 100 ml). The combined organic extracts were washed with brine, dried (MgSO₄) and concentrated *in vacuo* to give the crude diols as an inseparable mixture (1.5:1) of diastereoisomers which were used immediately in the next step. The isomeric ratio was ascertained by integration of the crude mixture which revealed signals derived from one of the C9 protons at δ 4.82 (dd, *J* 12.2, 1.2, minor) and 4.60 ppm (dd, *J* 12.1, 1.2, minor) in the ¹H NMR spectrum (360 MHz, CDCl₃).

tert-Butyldimethylsilyl chloride (1.72 g, 11.45 mmol) was added in one portion to a stirred solution of crude mixture of diols, triethylamine (1.6 ml, 11.0 mmol) and DMAP (70 mg, 0.58 mmol) in CH₂Cl₂ (25 ml) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h and at rt for 2 h. Saturated aqueous NaHCO₃ (40 ml) was added and the resulting mixture was extracted with CH₂Cl₂ (3 x 100 ml). The combined organic extracts were dried (MgSO₄) and concentrated *in vacuo*. The residue was purified by column chromatography (SiO₂, 30–40% Et₂O in hexanes) to give a mixture of **6.15a** and **6.15b** (2.7 g, 5.3 mmol, 95% from the alkene). Separation by chromatography on silica gel (0–50% Et₂O in hexanes) gave the desired monoprotected diol **6.15a** (1.5 g, 3.0 mmol, 53%) which crystallised on standing and the undesired monoprotected diol **6.15b** (1.0 g, 2.0 mmol, 36%) as a colourless oil. TLC monitoring conditions: 50% Et₂O in hexanes (phosphomolybdic acid); R_f (diol) 0.00 (black); R_f (**6.15a**) 0.43 (black), (**6.15b**) 0.31 (black).

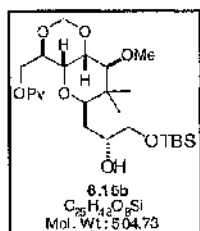
(1*R*,5*R*,6*R*,8*R*,10*S*)-5-(*tert*-Butylcarbonyloxy)methyl-8-[(2*S*)-3-[(*tert*-butyldimethylsilyl)oxy]-2-hydroxypropyl]-10-methoxy-9,9-dimethyl-2,4,7-trioxabicyclo[4.4.0]decane (**6.15a**)



mp 32–34 °C (hexanes–Et₂O); $[\alpha]_{\text{D}}^{23} +58.0$ (c 0.42, CHCl₃); ν_{max} film/cm^{–1} 3542, 2958, 1186, 1732, 1472, 1040; δ_{H} (400 MHz, CDCl₃): 5.00 (1H, d, *J* 6.6, OCH_AH_BO), 4.86 (1H, d, *J* 6.6, OCH_AH_BO), 4.54 (1H, dd, *J* 12.0, 1.7, C9H_AH_B), 4.22 (1H, ddd, *J* 10.5, 6.4, 1.7, C10H), 4.17 (1H, dd, *J* 12.0, 6.8, C9H_AH_B), 4.14 (1H, dd, *J* 12.4, 6.4, C12H), 4.00 (1H, dd, *J* 10.6, 6.8, C11H), 3.79 (1H, m, C17H), 3.62 (1H, dd, *J* 10.0, 5.2, C18H_AH_B), 3.57 (3H, s, OMe), 3.52–3.43 (3H, m, C13H, C15H and C18H_AH_B), 3.12 (1H, br d, *J* 1.6, OH), 1.82 (1H, ddd, *J* 14.5, 3.6, 2.0, C16H_AH_B), 1.44 (1H, ddd, *J* 14.5, 10.0, 8.0, C16H_AH_B), 1.23 (9H, s,

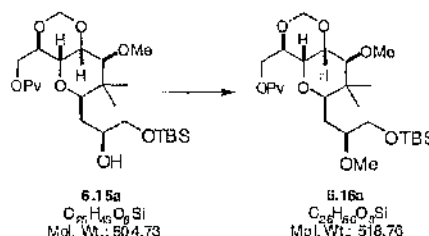
$^1\text{BuC=O}$), 1.00 (3H, s, C14Me), 0.90 (3H, s, C14Me), 0.89 (9H, s, $^t\text{BuSi}$), 0.07 (6H, s, Me_2Si); δ_{C} (100 MHz, CDCl_3): 178.3 (0, ester C=O), 86.9 (2, OCH_2O), 78.92 (1, C13 or C15), 78.87 (1, C15 or C13), 73.1 (1, C12), 71.7 (1, C17), 71.2 (1, C10), 67.4 (1, C11), 66.4 (2, C18), 63.4 (2, C9), 61.7 (3, OMe), 41.7 (0, C14 or CMe_3), 38.8 (0, CMe_3 or C14), 32.2 (2, C16), 27.1 (3, 3C, ^tBu), 25.8 (3, 3C, $^t\text{BuSi}$), 23.1 (3, C14Me), 18.2 (0, CSi), 13.4 (3, C14Me), -5.4 (3, 2C, SiMe_2); m/z (CI, isobutane) 505 $[(\text{M}+\text{H})^+]$, 100%. Found: $(\text{M}+\text{H})^+$, 505.3193. $\text{C}_{25}\text{H}_{49}\text{O}_8\text{Si}$ requires M , 505.3197. Found: C, 59.29; H, 9.53%. $\text{C}_{25}\text{H}_{48}\text{O}_8\text{Si}$ requires C, 59.49; H, 9.59.

(1*R*,5*R*,6*R*,8*R*,10*S*)-5-(*tert*-Butylcarbonyloxy)methyl-8-[(2*R*)-3-[(*tert*-butyldimethylsilyl)oxy]-2-hydroxypropyl]-10-methoxy-9,9-dimethyl-2,4,7-trioxabicyclo[4.4.0]decane (6.15b)



$[\alpha]_{\text{D}}^{23} +75.3$ (c 0.3, CHCl_3); ν_{max} film/ cm^{-1} 3568, 2958, 1186, 1732, 1472, 1040; δ_{H} (400 MHz, CDCl_3): 5.00 (1H, d, J 6.6, $\text{OCH}_A\text{H}_B\text{O}$), 4.86 (1H, d, J 6.6, $\text{OCH}_A\text{H}_B\text{O}$), 4.66 (1H, dd, J 12.1, 1.3, $\text{C9H}_A\text{H}_B$), 4.22–4.15 (1H, m, C10H collapsed by C12H), 4.19 (1H, dd, J 10.3, 7.1, C12H), 4.03 (1H, dd, J 12.1, 6.9, $\text{C9H}_A\text{H}_B$), 3.95 (1H, dd, J 11.0, 7.0, C11H), 3.85–3.75 (1H, m, C17H), 3.62 (1H, dd, J 9.8, 2.4, C15H), 3.57 (3H, s, OMe), 3.57 (1H, dd, J 9.9, 4.4, $\text{C18H}_A\text{H}_B$), 3.47 (1H, d, J 10.5, C13H), 3.47 (1H, dd, J 10.0, 3.3, $\text{C18H}_A\text{H}_B$), 3.13 (1H, br d, J 4.0, OH), 1.45–1.33 (2H, m, C16H₂), 1.23 (9H, s, $^t\text{BuC=O}$), 0.99 (3H, s, C14Me), 0.90 (9H, s, $^t\text{BuSi}$), 0.86 (3H, s, C14Me), 0.07 (6H, s, Me_2Si); δ_{C} (100 MHz, CDCl_3): 178.8 (0, COO), 86.9 (2, OCH_2O), 79.4 (1, C13), 74.0 (1, C15), 73.6 (1, C10 or C12), 71.7 (1, C12 or C10), 67.9 (1, C17), 67.8 (2, C18), 67.3 (1, C11), 64.0 (2, C9), 61.8 (3, OMe), 41.3 (0, C14 or CMe_3), 38.9 (0, CMe_3 or C14), 32.0 (2, C16), 27.1 (3, 3C, ^tBu), 25.9 (3, 3C, $^t\text{BuSi}$), 22.9 (3, C14Me), 18.3 (0, CSi), 13.2 (3, C14Me), -5.3 (3, 2C, SiMe_2); m/z (CI, isobutane) 505 $[(\text{M}+\text{H})^+]$, 100%, 487 (8), 447 (10). Found: $(\text{M}+\text{H})^+$, 505.3193. $\text{C}_{25}\text{H}_{49}\text{O}_8\text{Si}$ requires M , 505.3197. Found: C, 59.58; H, 9.40%. $\text{C}_{25}\text{H}_{48}\text{O}_8\text{Si}$ requires C, 59.49; H, 9.59.

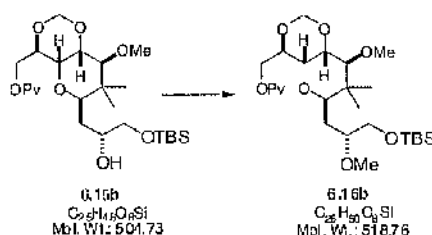
(1*R*,5*R*,6*R*,8*R*,10*S*)-5-(*tert*-Butylcarbonyloxy)methyl-8-[(2*S*)-3-[(*tert*-butyldimethylsilyl)oxy]-2-methoxypropyl]-10-methoxy-9,9-dimethyl-2,4,7-trioxabicyclo[4.4.0]decane (6.16a)



A solution of alcohol 6.15a (525 mg, 1.04 mmol), 2,6-di-*tert*-butyl-4-methylpyridine (700 mg, 3.36 mmol) and methyl trifluoromethanesulfonate (350 μl , 3.05 mmol) in toluene (3 ml) was stirred at 70 $^{\circ}\text{C}$ (oil bath temperature) for 4 h and overnight at 40 $^{\circ}\text{C}$. The reaction mixture was cooled to rt and treated with saturated aqueous NaHCO_3 and extracted with Et_2O (3 x 20 ml). The combined organic extracts were washed with

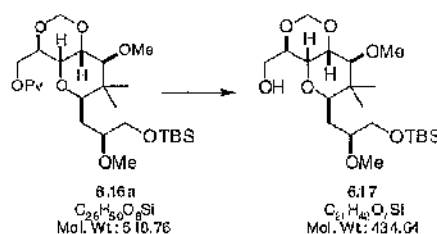
aqueous HCl (2M) and brine, then dried (Na₂SO₄) and concentrated *in vacuo*. The residue was purified by column chromatography (SiO₂, 5–25% Et₂O in hexanes) to give methyl ether **6.16a** (412 mg, 0.794 mmol, 76%) as a colourless oil which solidified on standing: mp 30–32 °C (hexanes–Et₂O); [α]_D²¹ +91.4 (*c* 0.3, CHCl₃); ν_{\max} KBr/cm⁻¹ 2958, 1732, 1472, 1108; δ_{H} (400 MHz, CDCl₃): 5.01 (1H, d, *J* 6.6, OCH_AH_BO), 4.86 (1H, d, *J* 6.6, OCH_AH_BO), 4.46 (1H, dd, *J* 10.1, 5.5, C9H_AH_B), 4.20–4.11 (3H, m, C9H_AH_B, C10H, C12H), 4.00 (1H, dd, *J* 10.2, 6.8, C11H), 3.67 (2H, d, *J* 4.3, C18H₂), 3.57 (3H, s, OMe), 3.43 (1H, d, *J* 10.3, C13H), 3.36 (3H, s, OMe), 3.35 (1H, dd, *J* 9.8, 1.6, C15H), 3.29 (1H, dq, *J* 8.1, 4.3, C17H), 1.81 (1H, ddd, *J* 14.2, 8.1, 1.6, C16H_AH_B), 1.52 (1H, ddd, *J* 14.2, 7.6, 10.1, 4.3, C16H_AH_B), 1.23 (9H, s, ^tBuC=O), 1.00 (3H, s, C14Me), 0.90 (9H, s, ^tBuSi), 0.89 (3H, s, C14Me), 0.07 (6H, s, Me₂Si); δ_{C} (100 MHz, CDCl₃): 178.4 (0, ester C=O), 87.0 (2, OCH₂O), 79.8 (1, C17), 79.5 (1, C13), 76.2 (1, C15), 73.4 (1, C10 or C12), 71.4 (1, C12 or C10), 67.3 (1, C11), 63.8 (2, C18 or C9), 63.6 (2, C9 or C18), 61.8 (3, OMe), 57.2 (3, OMe), 41.7 (0, C14 or CMe₃), 39.0 (0, CMe₃ or C14), 30.5 (2, C16), 27.3 (3, 3C, ^tBu), 26.1 (3, 3C, ^tBuSi), 23.4 (3, C14Me), 18.4 (0, CSi), 13.5 (3, C14Me), -5.2 (3, 2C, Me₂Si); *m/z* (CI, isobutane) 519 [(M+H)⁺, 100%], 461 (8), 387 (10). Found: (M+H)⁺, 519.3350. C₂₆H₅₁O₈Si requires *M*, 519.3353. Found: C, 60.31; H, 9.63%. C₂₆H₅₁O₈Si requires C, 60.20; H, 9.71.

(1*R*,5*R*,6*R*,8*R*,10*S*)-5-(*tert*-Butylcarbonyloxy)methyl-8-[(*tert*-butyldimethylsilyl)oxy]-2-methoxypropyl]-10-methoxy-9,9-dimethyl-2,4,7-trioxabicyclo[4.4.0]decane (6.16b**)**



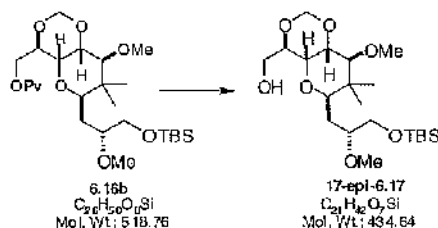
Methylation of **6.15b** (530 mg, 1.05 mmol) by the same procedure gave methyl ether **6.16b** (403 mg, 0.78 mmol, 74%) as a colourless oil: [α]_D¹⁹ +82.5 (*c* 0.8, CHCl₃); ν_{\max} KBr/cm⁻¹ 2957, 1732, 1473, 1111; δ_{H} (400 MHz, CDCl₃): 5.02 (1H, d, *J* 6.6, OCH_AH_BO), 4.85 (1H, d, *J* 6.6, OCH_AH_BO), 4.36–4.30 (1H, m, C9H_AH_B), 4.23 (1H, dd, *J* 10.4, 7.0, C9H_AH_B), 4.23–4.18 (1H, m collapsed by signals at 4.23 and 4.21 ppm, C10H), 4.16 (1H, dd, *J* 10.2, 6.9, C12H), 3.98 (1H, dd, *J* 10.4, 6.9, C11H), 3.63 (1H, dd, *J* 10.8, 4.6, C18H_AH_B), 3.60–3.54 (1H, m, C18H_AH_B), 3.56 (3H, s, OMe), 3.51 (1H, dd, *J* 10.1, 1.0, C15H), 3.47 (1H, d, *J* 10.3, C13H), 3.37 (3H, s, OMe), 3.38–3.31 (1H, m, C17H), 1.52 (1H, ddd, *J* 14.3, 10.4, 1.4, C16H_AH_B), 1.40 (1H, ddd, *J* 14.4, 10.4, 2.3, C16H_AH_B), 1.21 (9H, s, ^tBuC=O), 0.97 (3H, s, C14Me), 0.88 (9H, s, ^tBuSi), 0.85 (3H, s, C14Me), 0.04 (6H, s, Me₂Si); δ_{C} (100 MHz, CDCl₃): 178.2 (0, ester C=O), 86.8 (2, OCH₂O), 79.4 (1, C13), 77.6 (1, C17), 74.0 (1, C15), 73.5 (1, C12), 71.3 (1, C10), 67.0 (1, C11), 64.5 (2, C18), 63.6 (2, C9), 61.7 (3, OMe), 57.4 (3, OMe), 41.2 (0, C14 or CMe₃), 38.8 (0, CMe₃ or C14), 31.5 (2, C16), 27.1 (3, 3C, ^tBu), 25.8 (3, 3C, ^tBuSi), 23.1 (3, C14Me), 18.2 (0, CSi), 13.3 (3, C14Me), -5.4 (3, 2C, Me₂Si); *m/z* (CI, isobutane) 519 [(M+H)⁺, 80%], 487 (60), 461 (10), 387 (10), 355 (100), 315 (15). Found: (M+H)⁺, 519.3352. C₂₆H₅₁O₈Si requires *M*, 519.3353. Found: C, 60.28; H, 9.59%. C₂₆H₅₀O₈Si requires C, 60.20; H, 9.71.

(1*R*,5*R*,6*R*,8*R*,10*S*)-8-[(2*S*)-3-[(*tert*-Butyldimethylsilyl)oxy]-2-methoxypropyl]-5-hydroxymethyl-10-methoxy-9,9-dimethyl-2,4,7-trioxabicyclo[4.4.0]decane (6.17)



To a solution of ester **6.16a** (415 mg, 0.800 mmol) in THF (5 ml) at $-80\text{ }^{\circ}\text{C}$ was added Red-AlTM (400 μl , 1.1 M in THF, 0.44 mmol) dropwise over 5 min. The cooling bath was removed and the clear colourless reaction mixture allowed to warm to $0\text{ }^{\circ}\text{C}$ over 30 min whereupon acetone (40 μl) was added and the mixture then poured onto ice cold aqueous NaOH (1M, 1.9 ml). Dichloromethane (2 ml) and H_2O (2 ml) were added and the clear colourless phases were then separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 30 ml). The combined organic extracts were dried (MgSO_4) and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2 , 40% Et_2O in hexanes) to give alcohol **6.17** (327 mg, 0.75 mmol, 94%) as a clear colourless oil: $[\alpha]_{\text{D}}^{21} +67.4$ (c 1.6, CHCl_3); ν_{max} film/ cm^{-1} 3466, 2932, 1472; δ_{H} (400 MHz, CDCl_3): 5.02 (1H, d, J 6.5, $\text{OCH}_A\text{H}_B\text{O}$), 4.85 (1H, d, J 6.5, $\text{OCH}_A\text{H}_B\text{O}$), 4.14 (1H, dd, J 10.3, 6.0, C11H), 4.20–3.80 (2H, m, C10H, C12H), 3.85 (1H, br d, J 11.7, C9H_AH_B), 3.73–3.66 (1H, m, C9H_AH_B), 3.65 (1H, dd, J 10.8, 4.7, C18H_AH_B), 3.59 (1H, dd, J 10.8, 4.5, C18H_AH_B), 3.56 (3H, s, OMe), 3.42 (1H, d, J 10.4, C13H), 3.36 (3H, s, OMe), 3.37–3.33 (1H, m, C15H), 3.28 (1H, dq, J 7.6, 4.4, C17H), 2.48 (1H, br s, OH), 1.76 (1H, ddd, J 14.4, 7.6, 1.6, C16H_AH_B), 1.49 (1H, ddd, J 14.4, 9.6, 4.8, C16H_AH_B), 0.97 (3H, s, C14Me), 0.89 (9H, s, ^{*t*}BuSi), 0.86 (3H, s, C14Me), 0.06 (6H, s, Me₂Si); δ_{C} (100 MHz, CDCl_3): 86.7 (2, OCH_2O), 79.9 (1, C17), 79.2 (1, C13), 76.0 (1, C15), 73.3 (1, C10 or C11 or C12), 73.2 (1, C10 or C11 or C12), 68.0 (1, C10 or C12), 63.9 (2, C18), 63.4 (2, C9), 61.7 (3, OMe), 57.0 (3, OMe), 41.7 (0, C14), 30.5 (2, C16), 25.8 (3, 3C, ^{*t*}BuSi), 23.2 (3, C14Me), 18.2 (0, CSi), 13.1 (3, C14Me), -5.4 (3, 2C, Me₂Si); m/z (CI, isobutane) 435 $[(\text{M}+\text{H})^+]$, 100%, 403 (12), 377 (15), 345 (4), 303 (23). Found: $(\text{M}+\text{H})^+$, 435.2779. $\text{C}_{21}\text{H}_{42}\text{O}_7\text{Si}$ requires M , 435.2778. Found: C, 58.08; H, 9.73%. $\text{C}_{21}\text{H}_{42}\text{O}_7\text{Si}$ requires C, 58.03; H, 9.74.

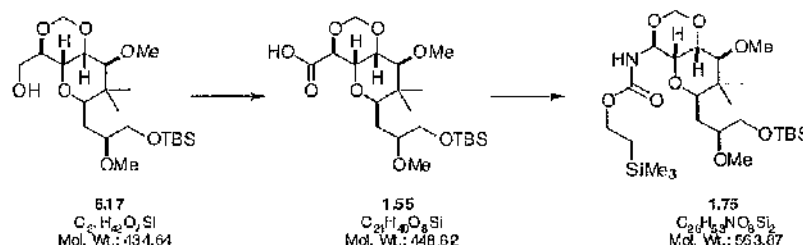
17-*epi*-6.17



Reductive cleavage of pivalate ester **6.16b** (320 mg, 0.62 mmol) by the same procedure afforded alcohol **17-*epi*-6.17** (264 mg, 0.61 mmol, 98%) as a clear colourless oil: $[\alpha]_{\text{D}}^{22} +92.0$ (c 1.5, CHCl_3); ν_{max} film/ cm^{-1} 3466, 2930, 1470; δ_{H} (400 MHz, CDCl_3): 5.02 (1H, d, J 6.5, $\text{OCH}_A\text{H}_B\text{O}$), 4.83 (1H, d, J 6.5, $\text{OCH}_A\text{H}_B\text{O}$), 4.13 (1H, dd, J 10.3, 6.8, C12H), 4.05 (1H, ddd, J 10.6, 5.5, 2.5, C10H), 3.96 (1H, dd, J 10.6, 6.9, C11H), 3.89–3.81 (1H, m, C9H_AH_B), 3.71–3.64 (1H, m, C9H_AH_B), 3.62–3.55 (2H, m, C18H₂), 3.53 (3H, s, OMe), 3.49 (1H, d, J 10.3, C13H), 3.43 (1H, d, J 10.4, C15H), 3.39 (3H, s, OMe), 3.37–3.30 (1H, m, C17H), 2.54 (1H, br s, OH), 1.53–1.45 (1H, m, C16H_AH_B), 1.40–1.30 (1H, m, C16H_AH_B), 0.93 (3H, s, C14Me), 0.86 (9H, s, ^{*t*}BuSi), 0.82 (3H, s, C14Me), 0.02 (6H, s, Me₂Si); δ_{C} (100 MHz, CDCl_3): 86.6 (2, OCH_2O), 79.4 (1,

C15), 77.8 (1, C17), 73.9 (1, C13), 73.5 (1, C10 or C12), 73.4 (1, C10 or C12), 67.4 (1, C11), 64.7 (2, C18), 62.8 (2, C9), 61.6 (3, OMe), 57.5 (3, OMe), 41.2 (0, C14), 31.2 (2, C16), 25.8 (3, 3C, ^tBuSi), 23.0 (3, C14Me), 18.2 (0, CSi), 13.1 (3, C14Me), -5.5 (3, 2C, Me₂Si); *m/z* (CI, isobutane) 435 [(M+H)⁺, 100%], 403 (12), 377 (10), 345 (4), 303 (23). Found: (M+H)⁺, 435.2777. C₂₆H₄₃O₇Si requires *M*, 435.2778. Found: C, 58.12; H, 9.68%. C₂₁H₄₂O₇Si requires C, 58.03; H, 9.74.

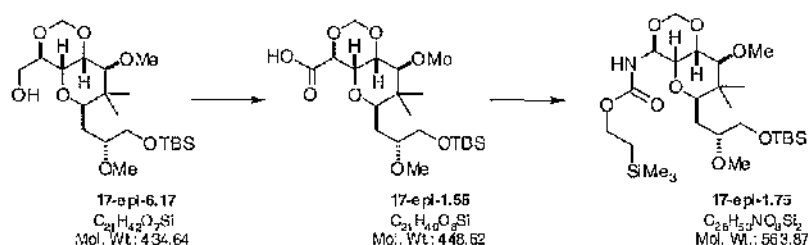
(1*R*,5*S*,6*S*,8*R*,10*S*)-8-[(2*S*)-3-[(*tert*-Butyldimethylsilyl)oxy]-2-methoxypropyl]-10-methoxy-9,9-dimethyl-5-*N*-[(2-trimethylsilyl)ethoxycarbonyl]amino]-2,4,7-trioxabicyclo[4.4.0]decane (**1.75**) via Curtius rearrangement



Sodium periodate (750 mg, 3.5 mmol) was added to a stirred mixture of alcohol **6.17** (280 mg, 0.65 mmol), carbon tetrachloride (5 ml), acetonitrile (5 ml) and water (7.5 ml) followed by ruthenium chloride trihydrate (11.3 mg, 0.043 mmol). The reaction mixture was stirred at rt for 3 h and extracted with CH₂Cl₂ (3 x 10 ml). The combined organic extracts were dried (MgSO₄) and concentrated *in vacuo*. The crude black-green residue was dissolved in anhydrous toluene (2 ml) and concentrated *in vacuo* three times and then immediately used in the next step.

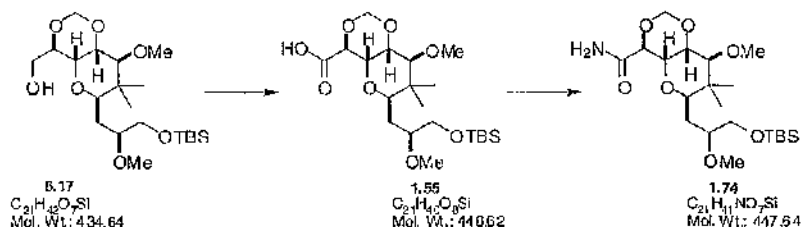
The crude acid **1.55** was dissolved in anhydrous toluene (3 ml) to which freshly activated 4Å molecular sieves (80 mg) and anhydrous *N*-ethyldiisopropylamine (0.180 ml, 1.03 mmol) were added. 2-Trimethylsilylethanol (0.73 ml, 5.1 mmol), dried by the addition of freshly activated 4Å molecular sieves (80 mg), and diiphenylphosphoryl azide (0.18 ml, 0.83 mmol) were then added. The mixture was plunged into an oil bath at 65 °C and evolution of N₂ gas was observed. After heating at 65 °C for 3 h the reaction mixture was quenched by the addition of saturated aqueous NaHCO₃ (15 ml) and extracted with CH₂Cl₂ (3 x 20 ml). The combined organic extracts were dried (Na₂SO₄) and concentrated *in vacuo*. The residue was purified by column chromatography (SiO₂, 5–25% Et₂O in hexane) to give carbamate **1.75** (205 mg, 0.364 mmol, 56%) as a pale yellow oil: [α]_D¹⁸ +56.6 (c 0.73, CHCl₃); *v*_{max} (CDCl₃)/cm⁻¹ 3437, 2959, 1729, 1514, 1212; δ_H (400 MHz, CDCl₃): 5.51 (1H, br t, *J* 9.3, C10H), 5.32 (1H, d, *J* 9.3, NH), 5.14 (1H, d, *J* 6.7, OCH_AH_BO), 4.85 (1H, d, *J* 7.0, OCH_AH_BO), 4.25–4.15 (3H, m, C12H and OCH₂CH₂TMS), 3.80 (1H, dd, *J* 9.5, 6.9, C11H), 3.63 (1H, dd, *J* 11.1, 3.5, C18H_AH_B), 3.56 (1H, dd, *J* 10.8, 4.0, C18H_AH_B), 3.56 (3H, s, OMe), 3.43 (1H, d, *J* 10.3, C13H), 3.32 (3H, s, OMe), 3.29 (1H, d, *J* 9.5, C15H), 3.18 (1H, dq, *J* 7.8, 4.0, C17H), 1.84 (1H, dd, *J* 13.2, 8.0, C16H_AH_B), 1.47 (1H, m, C16H_AH_B), 1.05–0.95 (2H, m, CH₂TMS), 0.99 (3H, s, C14Me), 0.89 (9H, s, ^tBuSi), 0.88 (3H, s, C14Me), 0.06 (6H, s, Me₂Si), 0.05 (9H, s, Me₃Si); δ_C (90 MHz, CDCl₃): 155.8 (0, O–C(O)–NH), 86.3 (2, OCH₂O), 79.7 (1, C17), 79.6 (1, C13), 76.5 (1, C10 or C15), 76.3 (1, C10 or C15), 74.4 (1, C12), 70.3 (1, C11), 63.9 (2, OCH₂CH₂TMS), 62.1 (2, C18), 61.8 (3, OMe), 56.9 (3, OMe), 41.7 (0, C14), 29.7 (2, C16), 25.9 (3, 3C, ^tBuSi), 23.3 (3, C14Me), 18.3 (0, CSi), 17.7 (2, CH₂Si), 13.4 (3, C14Me), -1.5 (3, 3C, Me₃Si), -5.4 (3, 2C, Me₂Si); *m/z* (CI, isobutane) 564 [(M+H)⁺, 20%], 536 (100), 488 (25), 372 (25). Found: (M+H)⁺, 564.3385. C₂₆H₅₄NO₈Si₂ requires *M*, 564.3388.

(1*R*,5*S*,6*S*,8*R*,10*S*)-8-[(2*R*-3-[(*tert*-Butyldimethylsilyl)oxy]-2-methoxypropyl)-10-methoxy-9,9-dimethyl-5-[*N*-[(2-trimethylsilyl)ethoxycarbonyl]amino]-2,4,7-trioxabicyclo[4.4.0]decane (17-*epi*-1.75)



Alcohol **17-*epi*-6.17** (258 mg, 0.59 mmol) was converted to carbamate **17-*epi*-1.75** (192 mg, 0.340 mmol, 57%) by the same procedure $[\alpha]_D^{19} +65.0$ (c 0.4, $CHCl_3$). ν_{max} ($CDCl_3$)/ cm^{-1} 3322, 2953, 1729; δ_H (400 MHz, $CDCl_3$): 5.52 (1H, br t, J 8.5, C10H), 5.36 (1H, d, J 8.3, NH), 5.14 (1H, d, J 6.7, OCH_AH_BO), 4.85 (1H, d, J 7.0, OCH_AH_BO), 4.24–4.17 (2H, m, C12H and $OCH_AH_BCH_2TMS$), 4.17–4.05 (1H, m, $OCH_AH_BCH_2TMS$), 3.80 (1H, br t, J 8.5, C11H), 3.61–3.53 (2H, m, C18H₂), 3.56 (3H, s, OMe), 3.51–3.40 (2H, m, C13H and C15H), 3.49 (3H, s, OMe), 3.31–3.25 (1H, m, C17H), 1.48–1.35 (2H, m, C16H₂), 0.98 (3H, s, C14Me), 0.98–0.93 (2H, m, CH_2TMS), 0.89 (9H, s, $tBuSi$), 0.84 (3H, s, C14Me), 0.045 and 0.032 (15H, 2 x s, Me_2Si and Me_3Si); δ_C (100 MHz, $CDCl_3$): 155.9 (0, N–C=O), 86.1 (2, OCH_2O), 79.6 (1, C13 or C15), 78.3 (1, C17), 76.3 (1, C10), 74.9 (1, C13 or C15), 74.4 (1, C12), 70.2 (1, C11), 65.2 (2, OCH_2-CH_2TMS), 63.8 (2, C18), 61.8 (3, OMe), 58.1 (3, OMe), 41.3 (0, C14), 31.9 (2, C16), 25.9 (3, 3C, $tBuSi$), 23.1 (3, C14-Me), 18.3 (0, CSi), 17.7 (2, CH_2TMS), 13.4 (3, C14Me), –1.6 (3, 3C, $SiMe_3$), –5.4 (3, 2C, $SiMe_2$); m/z (FAB mode, PEG) 564 $[(M+H)^+]$. Found: $(M+H)^+$, 564.3384. $C_{26}H_{54}NO_8Si_2$ requires M , 564.3388.

(1*R*,5*S*,6*S*,8*R*,10*S*)-5-Aminocarbonyl-8-[(2*S*)-3-[(*tert*-butyldimethylsilyl)oxy]-2-methoxypropyl]-10-methoxy-9,9-dimethyl-2,4,7-trioxabicyclo[4.4.0]decane (1.74)

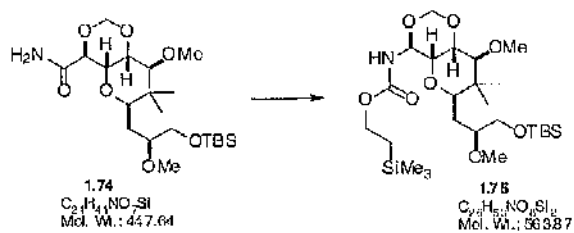


Sodium periodate (50 mg, 0.24 mmol) was added to a stirred mixture of alcohol **6.17** (21 mg, 0.048 mmol), carbon tetrachloride (0.3 ml), acetonitrile (0.3 ml) and a solution of ruthenium chloride trihydrate in water (6.7 mM, 0.45 ml, 0.003 mmol). The reaction mixture was stirred at rt for 5 h and extracted with CH_2Cl_2 (3 x 3 ml). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The crude black-green residue (24 mg) was immediately used in the next step.

To crude acid **1.55** in CH_2Cl_2 (0.5 ml) was added 1-hydroxybenzotriazole monohydrate (6.5 mg, 0.048 mmol) followed by a solution of 1,3-dicyclohexylcarbodiimide in CH_2Cl_2 (96 mM, 0.5 ml, 0.048 mmol) at rt. The reaction mixture was stirred for 1 h and ammonia (gas) was bubbled into the reaction mixture for 15 min to yield a white precipitate. The solution was filtered and the solid was washed with CH_2Cl_2 (4 ml). The combined filtrate was washed with saturated aqueous $NaHCO_3$ (3 ml), ice cooled HCl (0.1M, 3 ml), aqueous $NaHCO_3$ (3 ml), brine (3 ml), and then dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2 5g, 70–100% Et_2O in hexanes and then 0–50%

EtOAc in Et₂O) to give the desired amide **1.74** (19.3 mg, 0.043 mmol, 90%) as an oil: $[\alpha]_D^{24} +35.9$ (c 0.85, CHCl₃); ν_{max} (CDCl₃)/cm⁻¹ 3332, 2929, 1697; δ_{H} (400 MHz, CDCl₃): 6.65 (1H, s, NH_AH_B), 5.45 (1H, s, NH_AH_B), 5.06 (1H, d, *J* 6.5, OCH_AH_BO), 4.91 (1H, d, *J* 6.5, OCH_AH_BO), 4.39 (1H, d, *J* 8.0, C10H), 4.24 (1H, dd, *J* 7.8, 5.4, C11H), 4.05 (1H, dd, *J* 7.7, 5.2, C12H), 3.78 (1H, dd, *J* 11.1, 4.2, C18H_AH_B), 3.69 (1H, dd, *J* 11.1, 4.1, C18H_AH_B), 3.51 (3H, s, OMe), 3.51–3.46 (1H, m, C15H), 3.41–3.36 (1H, m, C17H), 3.37 (3H, s, OMe), 3.26 (1H, d, *J* 7.9, C13H), 1.85 (1H, ddd, *J* 14.5, 7.7, 2.4, C16H_AH_B), 1.79–1.64 (1H, m, C16H_AH_B), 1.08 (3H, s, C14Me), 0.91 (3H, s, C14Me), 0.90 (9H, s, ^tBuSi), 0.07 (6H, s, Me₂Si); δ_{C} (100 MHz, CDCl₃): 170.7 (O, H₂N–C=O), 87.4 (2, OCH₂O), 80.5 (1, C13), 79.7 (1, C17), 77.2 (1, C15), 73.4 (1, C10), 72.7 (1, C12), 67.0 (1, br, C11), 63.1 (2, C18), 61.6 (3, OMe), 57.1 (3, OMe), 49.1 (0, C14), 29.9 (2, C16), 24.9 (3, 3C, ^tBuSi), 24.5 (3, C14Me), 18.3 (0, CSi), 16.5 (3, br, C14Me), –5.317 (3, MeSi), –5.373 (3, MeSi); *m/z* (CI, isobutane) 448 [(M+H)⁺, 30%], 279 (20), 225 (100). Found: (M+H)⁺, 448.2729. C₂₁H₄₂NO₇Si requires *M*, 448.2731. Found: C, 56.40; H, 9.16; N, 3.12%. C₂₁H₄₁O₇Si requires C, 56.35; H, 9.23; N, 3.13

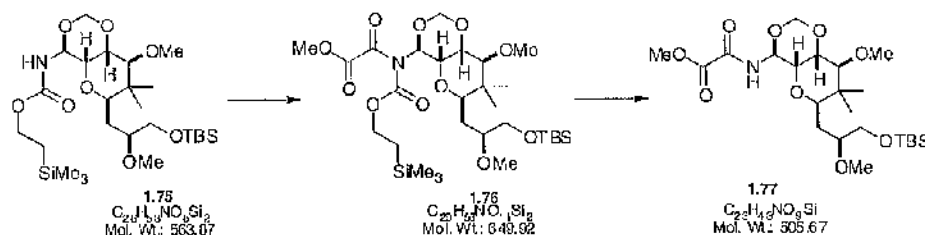
(1*R*,5*S*,6*S*,8*R*,10*S*)-8-[(2*S*)-3-[(*tert*-Butyldimethylsilyl)oxy]-2-methoxypropyl]-10-methoxy-9,9-dimethyl-5-[*N*-[(2-trimethylsilyl)ethoxycarbonyl]amino]-2,4,7-trioxabicyclo[4.4.0]decane (**1.75**) via Hofmann rearrangement.



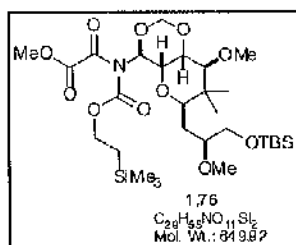
Procedure A: Trimethylsilylethanol (0.05 ml, 0.35 mmol), silver acetate (4.1 mg, 0.025 mmol) followed by *N*-bromosuccinimide (4.5 mg, 0.025 mmol) were added to a solution of amide **1.74** (8.1 mg, 18.1 μ mol) in *N,N*-dimethylformamide (1 ml) at rt. The reaction mixture was stirred at rt for 24 h, treated with saturated aqueous NaHCO₃ (1 ml) and extracted with hexanes–Et₂O (1:1) (3 x 3 ml). The combined organic extracts were dried (MgSO₄) and concentrated *in vacuo*. The residue was then purified by column chromatography (SiO₂, 0–30% Et₂O in hexanes) to give carbamate **1.75** (8.9 mg, 15.9 μ mol, 88%) as a pale yellow oil.

Procedure B: Trimethylsilylethanol (0.05 ml, 0.35 mmol), pyridine (2 μ l, 24.5 μ mol) followed by *l,l*-bis(trifluoroacetoxy)iodobenzene (Aldrich, 10.5 mg, 24.5 μ mol) were added to a solution of amide **1.74** (8.5 mg, 19.0 μ mol) in acetonitrile (0.1 ml) at rt. The reaction mixture was stirred at rt for 24 h, treated with saturated aqueous NaHCO₃ (2 ml) and extracted with CH₂Cl₂ (3 x 3 ml). The combined organic extracts were dried (MgSO₄) and concentrated *in vacuo*. The residue was then purified by column chromatography (SiO₂, 0–30% Et₂O in hexanes) to give carbamate **1.75** (8.6 mg, 15.3 μ mol, 81%) as a pale yellow oil.

(1*R*,5*S*,6*S*,8*R*,10*S*)-8-[(2*S*)-3-[(*tert*-Butyldimethylsilyloxy]-2-methoxypropyl]-10-methoxy-9,9-dimethyl-5-[*N*-(methyloxalyl)amino]-2,4,7-trioxabicyclo[4.4.0]decane (**1.77**)

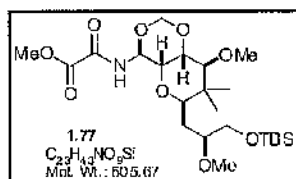


To a solution of DMAP (233 mg, 1.68 mmol) and methyl oxalyl chloride (140 μ l, 1.53 mmol) in CH₂Cl₂ (2 ml) was added to carbamate **1.75** (178 mg, 0.316 mmol) and the reaction mixture was stirred at rt for 6 d. The solution was then diluted with Et₂O (5 ml) and quickly washed with ice-cooled ammonia solution (0.1M, 10 ml) and then washed quickly with ice-cooled aqueous HCl solution (0.1M, 10 ml) and finally washed with saturated aqueous NaHCO₃ (10 ml). The organic phase was then dried (Na₂SO₄) and concentrated *in vacuo* to give the fairly pure *N*-Teoc amide **1.76** as a pale yellow oil (201 mg, 0.309 mmol, 98%) which was used crude in the next reaction. *N*-Teoc amide **1.76** was unstable towards column chromatography but a sample isolated in low yield (34%) gave the following spectroscopic data:



$[\alpha]_D^{20} +30.9$ (c 1.1, CHCl₃); ν_{\max} (film)/cm⁻¹ 2955, 2919, 2856, 1748, 1715, 1253; δ_H (400 MHz, CDCl₃): 6.12 (1H, d, *J* 10.4, C10H), 5.13 (1H, d, *J* 6.7, OCH_AH_BO), 4.97 (1H, d, *J* 6.7, OCH_AH_BO), 4.88 (1H, dd, *J* 10.4, 7.2, C11H), 4.39–4.36 (2H, m, OCH₂CH₂TMS), 4.32 (1H, dd, *J* 10.6, 7.2, C12H), 3.90 (3H, s, OMe), 3.66 (1H, dd, *J* 11.3, 3.3, C18H_AH_B), 3.59 (3H, s, OMe), 3.49 (1H, dd, *J* 11.3, 3.3, C18H_AH_B), 3.47 (1H, d, *J* 10.3, C13H), 3.31 (3H, s, OMe), 3.23 (1H, d, *J* 9.9, C15H), 3.14 (1H, dq, *J* 9.0, 3.0, C17H), 1.90 (1H, dd, *J* 14.0, 10.0, C16H_AH_B), 1.41 (1H, ddd, *J* 14.0, 10.2, 3.1, C16H_AH_B), 1.16–1.10 (2H, m, CH₂TMS), 0.97 (3H, s, C14Me), 0.90 (9H, s, *t*BuSi), 0.89 (3H, s, C14Me), 0.074 (6H, s, Me₂Si), 0.070 (9H, s, Me₃Si); δ_C (90 MHz, CDCl₃): 163.0 (0), 161.1 (0), 152.3 (0), 87.5 (2, OCH₂O), 79.2 (1, C13), 78.7 (1, C17), 76.9 (1, C10), 76.3 (1, C15), 74.8 (1, C12), 67.3 (2, CH₂CH₂TMS), 66.7 (1, C11), 61.4 (2, C18), 61.2 (3, OMe), 56.5 (3, OMe), 52.9 (3, OMe), 41.7 (0, C14), 30.0 (2, C16), 25.9 (3, 3C, *t*BuSi), 23.1 (3, C14Me), 18.3 (0, CSi), 17.3 (2, CH₂TMS), 13.1 (3, C14Me), -1.7 (3, 3C, Me₃Si), -5.40 (3, MeSi), -5.46 (3, MeSi); *m/z* (CI, isobutane) 650 [(M+H)⁺, 100%], 578 (70), 506 (50), 490 (50), 403 (70). Found: (M+H)⁺, 650.3393. C₂₉H₅₅NO₁₁Si₂ requires *M*, 650.3392. Found: C, 55.38; H, 9.52; N 2.24%. C₂₉H₅₅O₁₁Si₂ requires C, 55.38; H, 9.47; N, 2.48.

A solution of TBAF (0.76 g, 2.4 mmol) and acetic acid (0.5 ml, 8.8 mmol) in CH₂Cl₂ (9.5 ml) was added to the *N*-Teoc amide **1.76** and immediate gas evolution was observed. The reaction mixture was stirred for 4 min and then immediately diluted with CH₂Cl₂ (10 ml), and washed with water (3 x 10 ml). The organic phase was dried (MgSO₄) and concentrated *in vacuo*. The residue was then purified by column chromatography (SiO₂, 50–70% Et₂O in hexanes) to give **1.77** (116 mg, 0.230 mmol, 73%) as a white solid:



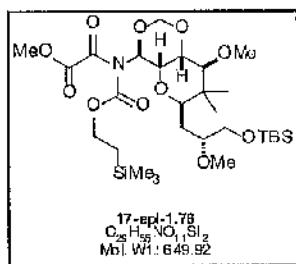
mp 136–138 °C (hexanes–ether); $[\alpha]_D^{20} +56.2$ (*c* 0.8, CHCl₃); ν_{\max} (CHCl₃)/cm⁻¹ 3401, 3019, 2956, 2884, 1720; δ_H (360 MHz, CDCl₃): 7.53 (1H, d, *J* 9.2, NH), 5.71 (1H, t, *J* 9.5, C10H), 5.16 (1H, d, *J* 7.0, OCH_AH_BO), 4.88 (1H, d, *J* 7.0, OCH_AH_BO), 4.23 (1H, dd, *J* 10.1, 6.6, C12H), 3.93 (1H, dd, *J* 9.5, 6.7, C11H), 3.93 (3H, s, OMe), 3.57 (1H, dd, *J* 10.8, 4.4, C18H_AH_B), 3.57 (3H, s, OMe), 3.52 (1H, dd, *J* 11.0, 4.1, C18H_AH_B), 3.43 (1H, d, *J* 10.2, C13H), 3.30 (1H, dd, *J* 9.6, 0.9, C15H), 3.27 (3H, s, OMe), 3.12 (1H, dq, *J* 8.2, 4.1, C17H), 1.82 (1H, ddd, *J* 14.3, 7.5, 1.4, C16H_AH_B), 1.47 (1H, ddd, *J* 14.5, 9.9, 4.2, C16H_AH_B), 1.00 (3H, s, C14Me), 0.88 (12H, s, ^tBuSi and C14Me), 0.05 (6H, s, Me₂Si); δ_C (90 MHz, CDCl₃): 160.2 (0, C(O)), 156.4 (0, C(O)), 86.4 (2, OCH₂O), 79.7 (1, C17), 79.4 (1, C13), 76.7 (1, C15), 74.2 (1, C12), 74.0 (1, C10), 69.9 (1, C11), 62.7 (2, C18), 61.7 (3, OMe), 56.8 (3, OMe), 53.9 (3, OMe), 41.6 (0, C14), 29.7 (2, C16), 25.8 (3, 3C, ^tBuSi), 23.3 (3, C14Me), 18.2 (0, CSi), 13.5 (3, C14Me), -5.5 (3, 2C, Me₂Si); *m/z* (CI, isobutane) 506 [(M+H)⁺, 100%], 474 (25), 448 (20), 444 (10), 374 (15). Found: (M+H)⁺, 506.2782. C₂₃H₄₄NO₉Si requires *M*, 506.2785. Found: C, 54.09; H, 8.29; N 2.69%. C₂₃H₄₃NO₉Si requires C, 54.63; H, 8.57; N, 2.77.

The structure and relative stereochemistry of **1.77** was confirmed by X-ray crystallography with Mo X-rays on a CAD4 diffractometer.^{136, 137} Crystal data (**1.77**) C₂₃H₄₃NO₉Si, *M* = 505.67, orthorhombic, *a* = 9.824(2), *b* = 12.368(2), *c* = 22.340(6) Å, *U* = 2934(1) Å³, *T* = 293 K, space group P2₁2₁2₁, *Z* = 4, μ (Mo-K α) 0.13 mm⁻¹, 10536 reflections measured, 3588 unique (*R*_{int} = 0.052) used in refinement. *R*1[2369 with *I* > 2 σ (*I*)] = 0.083, *wR*2(all data) = 0.27. The absolute structure could not be determined from the X-ray data. The results for **1.77** reflect the poor quality of the crystals. The atoms of the C15 side-chain show large *U*_{eq} values and some atypical bond lengths which suggest positional disorder. CCDC reference number 207/406. See <http://www.rsc.org/suppdata/p1/a9/a909898d/> for crystallographic files in .cif format.

17-epi-1.77

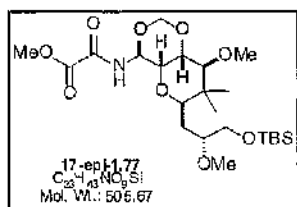
Acylation of carbamate **17-epi-1.75** (190 mg, 0.337 mmol) by the same procedure described above gave the *N*-Teoc amide **17-epi-1.76** in 50% yield:

Cleavage of *N*-Teoc amide **17-epi-1.76** by the same procedure described above gave recovered carbamate **17-epi-1.75** (29 mg, 0.052 mmol, 15%) and **17-epi-1.77** (106 mg, 0.230 mmol, 63%) as an oil:



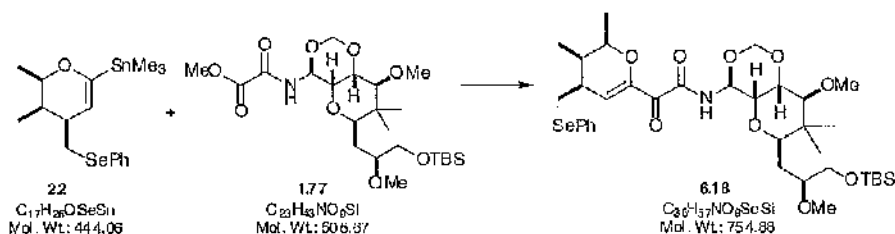
$[\alpha]_D^{24} +74.2$ (*c* 1.1, CHCl₃); ν_{\max} (CDCl₃)/cm⁻¹ 2954, 2922, 2857, 1749, 1715, 1252, 1109, 1026, 837, 775; δ_H (400 MHz, CDCl₃): 6.13 (1H, d, *J* 10.4, C10H), 5.13 (1H, d, *J* 6.7, OCH_AH_BO), 4.96 (1H, d, *J* 6.7,

OCH_AH_BO), 4.89 (1H, dd, *J* 10.4, 7.3, C11H), 4.40–4.35 (2H, m, OCH₂CH₂TMS), 4.32 (1H, dd, *J* 10.6, 7.3, C12H), 3.89 (3H, s, OMe), 3.62 (1H, dd, *J* 10.8, 4.5, C18H_AH_B), 3.59 (3H, s, OMe), 3.55 (1H, dd, *J* 10.8, 4.4, C18H_AH_B), 3.53–3.50 (2H, m, *J* 10.3, C13H and C15H), 3.34 (3H, s, OMe), 3.23–3.18 (1H, m, C17H), 1.52 (1H, dd, *J* 14.5, 9.4, C16H_AH_B), 1.41 (1H, ddd, *J* 14.6, 9.4, 2.3, C16H_AH_B), 1.15–1.10 (2H, m, CH₂TMS), 1.00 (3H, s, C14Me), 0.89 (9H, s, ^tBuSi), 0.85 (3H, s, C14Me), 0.073 (9H, s, Me₃Si), 0.044 (6H, s, Me₂Si); δ_C (90 MHz, CDCl₃): 162.9 (0), 161.1 (0), 152.6 (0), 87.5 (2, OCH₂O), 79.1 (1, C13 or C15), 77.8 (1, C17), 77.2 (1, C10), 75.6 (1, C15 or C13), 74.8 (1, C12), 67.6 (2, CH₂CH₂TMS), 66.3 (1, C11), 64.5 (2, C18), 61.8 (3, OMe), 57.2 (3, OMe), 52.9 (3, OMe), 41.5 (0, C14), 32.3 (2, C16), 25.9 (3, 3C, ^tBuSi), 23.1 (3, C14Me), 18.3 (0, C-Si), 17.3 (2, CH₂TMS), 13.2 (3, C14Me), –1.6 (3, 3C, Me₃Si), –5.38 (3, MeSi), –5.40 (3, MeSi); *m/z* (CI, isobutane) 650 [(M+H)⁺, 55%], 622 (70), 578 (60), 506 (35), 474 (45), 458 (25), 403 (70), 371 (45). Found: (M+H)⁺, 650.3387. C₂₉H₅₆NO₁₁Si₂ requires *M*, 650.3392.



[α]_D²³ +70.6 (c 1.5, CHCl₃); ν_{max} (CHCl₃)/cm^{–1} 3330, 2954, 2930, 2857, 1717, 1529, 1111, 1026, 836, 777; δ_H (360 MHz, CDCl₃): 7.56 (1H, d, *J* 9.1, NH), 5.73 (1H, t, *J* 9.4, C10H), 5.18 (1H, d, *J* 7.0, OCH_AH_BO), 4.87 (1H, d, *J* 7.0, OCH_AH_BO), 4.25 (1H, dd, *J* 10.3, 6.8, C12H), 3.96–3.90 (1H, m, C11H), 3.92 (3H, s, OMe), 3.60–3.52 (2H, m, C18H₂), 3.58 (3H, s, OMe), 3.52–3.46 (2H, m, C13H and C15H), 3.27 (3H, s, OMe), 3.22–3.17 (1H, m, C17H), 1.51–1.38 (2H, m, C16H₂), 1.00 (3H, s, C14Me), 0.88 (9H, s, ^tBuSi), 0.87 (3H, s, C14Me), 0.04 (6H, s, Me₂Si); δ_C (90 MHz, CDCl₃): 160.3 (0, C(O)), 156.4 (0, C(O)), 86.3 (2, OCH₂O), 79.5 (1, C13 or C15), 78.0 (1, C17), 75.2 (1, C13 or C15), 74.4 (1, C12), 74.1 (1, C10), 70.0 (1, C11), 64.8 (2, C18), 61.8 (3, OMe), 57.7 (3, OMe), 53.9 (3, OMe), 41.3 (0, C14), 31.7 (2, C16), 25.9 (3, 3C, ^tBuSi), 23.2 (3, C14Me), 18.2 (0, C-Si), 13.5 (3, C14Me), –5.5 (3, 2C, Me₂-Si); *m/z* (CI, isobutane) 506 [(M+H)⁺, 100%], 476 (15), 474 (10), 448 (10), 391 (7). Found: (M+H)⁺, 506.2785. C₂₃H₄₄NO₉Si requires *M*, 506.2785.

Formation of adduct 6.18

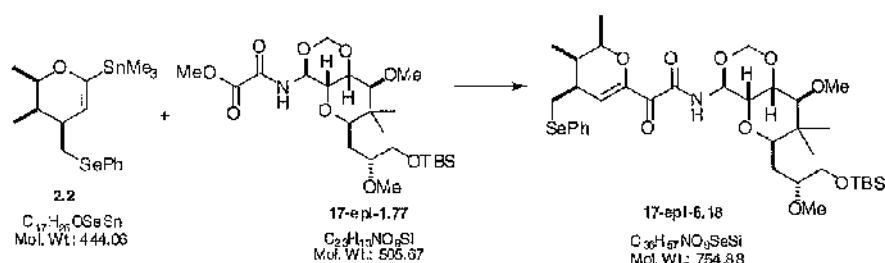


To a solution of stannane 2.2 (170 mg, 0.383 mmol) and 4Å MS in THF (2.5 ml) at –80 °C was added BuLi (265 µl, 1.43 M solution in hexane, 0.370 mmol) and the bright yellow solution stirred at –80 °C for 15 min. TMEDA (57 µl, 0.378 mmol) was added and after 10 min at –80 °C, a solution of ester 1.77 (73 mg, 0.144 mmol) and 4Å MS in THF (2.25 ml) was quickly added. After stirring for 1 h maintaining the temperature below –60 °C, the mixture was poured into brine (3 ml), and extracted with CH₂Cl₂ (2 x 5 ml). The combined extracts were dried (Na₂SO₄) and concentrated to give a yellow oil which was purified by column chromatography (SiO₂, PhMe:hexanes:EtOAc, 100:0:0, 0:95:5, 0:75:25, 0:50:50) to give (2*R*,3*R*,4*R*)-3,4-

dihydro-2,3-dimethyl-4-phenylselenenylmethyl-2*H*-pyran (77 mg, 0.274 mmol, 74%) and the coupling product **6.18** (44 mg, 0.058 mmol, 41% based on the fragment **1.77**) as a colourless oil: $[\alpha]_D^{24} +29.0$ (c 0.9, CHCl_3); ν_{max} (CHCl_3)/ cm^{-1} 3054, 2974, 2933, 2878, 1640, 1578, 1477, 1454, 1437, 1382, 1237, 1091, 736, 690; δ_{H} (400 MHz, CDCl_3): 7.43–7.40 (2H, m), 7.20–7.10 (3H, m), 6.21 (1H, dd, J 2.4, 6.2, C6H), 4.40 (1H, dt, J 1.7, 6.2, C5H), 3.92 (1H, dq, J 1.7, 6.6, C2H), 2.78 (1H, dd, J 9.1, 11.8, CH_AH_B), 2.73 (1H, dd, J 7.2, 11.8, CH_AH_B), 2.65–2.57 (1H, m, C4H), 1.83–1.75 (1H, m, C3H), 1.14 (3H, d, J 6.6, C2Me), 0.72 (3H, d, 7.0, C3Me); δ_{C} (100 MHz, CDCl_3): 143.8 (1, C6), 132.6 (1, 2C), 130.0 (0), 129.0 (1, 2C), 126.8 (1), 101.9 (1, C5), 75.3 (1, C2), 37.0 (1, C4), 34.0 (1, C3), 31.0 (2, CH_2Se), 18.2 (3, C2Me), 5.1 (3, C3Me). Found: $(\text{M}+\text{H})^+$, 282.0522. $\text{C}_{14}\text{H}_{18}\text{OSe}$ requires M , 282.0523.

Acyl dihydropyran **6.18**: $[\alpha]_D^{20} -21.2$ (c 0.5, CHCl_3); ν_{max} (CHCl_3)/ cm^{-1} 3319, 2928, 1671, 1106, 1023, 826; δ_{H} (400 MHz, CDCl_3): 7.56 (1H, d, J 9.5, NH), 7.55–7.51 (2H, m), 7.31–7.28 (3H, m), 7.14 (1H, t, J 1.8, C5H), 5.68 (1H, t, J 9.3, C10H), 5.16 (1H, d, J 6.9, $\text{OCH}_A\text{H}_B\text{O}$), 4.88 (1H, d, J 6.9, $\text{OCH}_A\text{H}_B\text{O}$), 4.23 (1H, dd, J 6.4, 9.9, C12H), 4.09 (1H, dq, J 1.2, 6.5, C2H), 3.95 (1H, dd, J 6.5, 9.3, C11H), 3.57 (3H, s, OMe), 3.57 (1H, dd, J 4.1, 10.9, C18 H_AH_B), 3.50 (1H, dd, J 3.8, 11.0, C18 H_AH_B), 3.42 (1H, d, J 10.0, C13H), 3.31 (1H, br d, J 9.3, C15H), 3.26 (3H, s, OMe), 3.10–3.16 (1H, m, C17H), 2.98–2.94 (2H, m, CH_2Se), 2.85 (1H, dddd, J 2.5, 5.7, 8.1, 10.6, C4H), 2.07–1.99 (1H, m, C3H), 1.83 (1H, ddd, J 1.4, 8.0, 14.1, C16 H_AH_B), 1.57–1.47 (1H, m, C16 H_AH_B), 1.39 (3H, d, J 6.5, C2Me), 1.01 (3H, s, C14Me), 0.90 (3H, s, C14Me), 0.88 (9H, s, $t\text{BuSi}$), 0.82 (3H, d, J 7.0, C3Me), 0.04 (6H, s, Me_2Si); δ_{C} (100 MHz, CDCl_3): 179.6 (0), 160.7 (0), 148.0 (0), 133.2 (1, 2C), 129.3 (1, 2C), 129.1 (0), 127.4 (1), 125.0 (1, C5), 86.4 (2, OCH_2O), 79.7 (1, C13 or C17), 79.4 (1, C17 or C13), 77.2 (1, C2 or C15), 76.8 (1, C15 or C2), 74.1 (1, C12), 73.8 (1, C10), 69.6 (1, C11), 62.3 (2, C18), 61.7 (3, OMe), 56.9 (3, OMe), 41.4 (0, C14), 39.0 (1, C4), 33.1 (1, C3), 29.5 (2, C16 or CH_2Se), 29.4 (2, CH_2Se or C16), 25.9 (3, 3C, $t\text{BuSi}$), 23.5 (3, C14Me), 18.3 (0, C5), 18.2 (3, C2Me), 13.9 (3, C14Me), 5.9 (3, C3Me), –5.30 (3, MeSi), –5.33 (3, MeSi); m/z (CI, isobutane) 756 $[(\text{M}+\text{H})^+]$, 30%, 698 (20), 598 (100), 540 (60). Found: $(\text{M}+\text{H})^+$, 756.3047. $\text{C}_{36}\text{H}_{58}\text{NO}_9\text{SeSi}$ requires M , 756.3045.

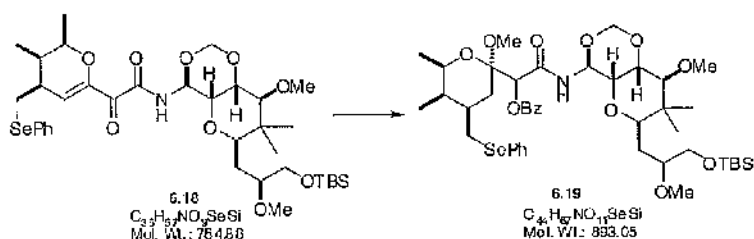
Formation of adduct 17-epi-6.18



Acylation of dihydropyran **2.2** (135 mg, 0.304 mmol) by the procedure described above gave (2*R*,3*R*,4*R*)-3,4-dihydro-2,3-dimethyl-4-phenylselenenylmethyl-2*H*-pyran (66 mg, 0.235 mmol, 77%) and the coupling product **17-epi-6.18** (36 mg, 0.048 mmol, 39% based on the right half fragment **17-epi-1.77**) as a colourless oil: $[\alpha]_D^{23} +16.0$ (c 1.0, CHCl_3); ν_{max} (CHCl_3)/ cm^{-1} 3366, 2928, 2855, 1727, 1670, 1104, 1024, 836; δ_{H} (400 MHz, CDCl_3): 7.63 (1H, d, J 8.7, NH), 7.52–7.45 (2H, m), 7.30–7.20 (3H, m), 7.15 (1H, t, J 1.8, C5H), 5.67 (1H, t, J 9.2, C10H), 5.14 (1H, d, J 7.0, $\text{OCH}_A\text{H}_B\text{O}$), 4.85 (1H, d, J 6.9, $\text{OCH}_A\text{H}_B\text{O}$), 4.21 (1H, dd, J 6.5, 10.2, C12H), 4.06 (1H, dq, J 1.3, 6.5, C2H), 3.93 (1H, dd, J 6.6, 9.5, C11H), 3.54 (3H, s, OMe), 3.52–3.43 (4H, m, C18 H_2 , C15H, C13H), 3.23–3.14 (1H, m, C17H), 3.19 (3H, s, OMe), 2.90–2.84 (2H, m, CH_2Se), 2.84–2.77 (1H, m, C4H), 2.10–1.92 (1H, m, C3H), 1.50–1.40 (1H, m, C16 H_AH_B), 1.30–1.18 (1H, m, C16 H_AH_B), 1.34 (3H, d, J 6.5, C2Me), 0.97 (3H, s, C14Me), 0.84 (9H, s, $t\text{BuSi}$), 0.83 (3H, s, C14Me),

0.73 (3H, d, J 7.0, C3Me), 0.00 (6H, s, Me₂Si); δ_{H} (400 MHz, C₆D₆): 7.49 (1H, d, J 9.0, NH), 7.35–7.32 (2H, m), 7.16 (1H, t, J 1.9, C5H), 6.97–6.91 (3H, m), 5.81 (1H, t, J 9.5, C10H), 4.68 (1H, d, J 6.9, OCH_AH_BO), 4.57 (1H, d, J 6.9, OCH_AH_BO), 4.19 (1H, dd, J 6.9, 10.4, C12H), 3.53–3.40 (5H, m), 3.38 (3H, s, OMe), 3.38–3.36 (1H, m), 3.19 (3H, s, OMe), 2.98 (1H, J 10.4, C13H), 2.59–2.51 (2H, m), 2.50–2.44 (1H, m), 1.61–1.53 (1H, m, C16H_AH_B), 1.48–1.40 (2H, m, C3H and C16H_AH_B), 0.95 (3H, d, J 6.7, C2Me), 0.91 (9H, s, ^tBuSi), 0.85 (3H, s, C14Me), 0.82 (3H, s, C14Me), 0.55 (3H, d, J 7.0, C3Me), 0.004 (3H, s, MeSi), –0.003 (3H, s, MeSi); δ_{C} (100 MHz, C₆D₆): 179.4 (0), 160.5 (0), 147.2 (0), 131.9 (1, 2C), 128.1 (1, 2C), 126.6 (0), 126.0 (1), 122.4 (1, C5), 84.9 (2, OCH₂O), 77.9 (1, C13), 77.0 (1), 75.0 (1), 73.8 (1), 73.7 (1, C12), 72.7 (1, C10), 68.9 (1), 63.5 (2, C18), 60.0 (3, OMe), 56.6 (3, OMe), 40.1 (0, C14), 37.7 (1), 32.0 (1), 31.0 (2, C16), 28.2 (2, CH₂Se), 24.8 (3, 3C, ^tBuSi), 21.6 (3, C14Me), 17.2 (0, CSi), 16.7 (3, C2Me), 12.2 (3, C14Me), 4.5 (3, C3Me), –6.47 (3, MeSi), –6.52 (3, MeSi); m/z (CI, isobutane) 756 [(M+H)⁺, 20%], 598 (100), 540 (20). Found: (M+H)⁺, 756.3049. C₃₆H₅₈NO₉SeSi requires M , 756.3045.

Synthesis of benzoate 6.19

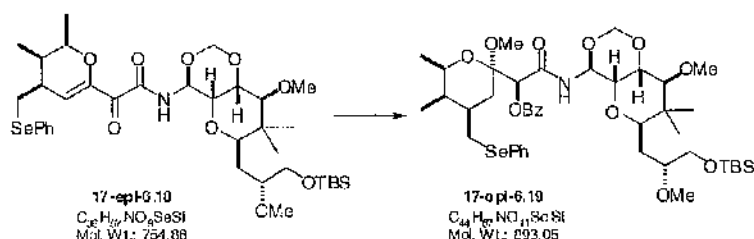


To a solution of acyldihydropyran **6.18** (30.0 mg, 39.7 μmol) in THF (2.5 ml) at -95°C was added dropwise LiBH(*s*-Bu)₃ (0.1 ml, 1.0 M solution in THF, 0.1 mmol). After 10 min at -95°C the mixture was treated with brine (1 ml) and extracted with CH₂Cl₂ (2 x 4 ml). The combined organic extracts were dried (Na₂SO₄) and concentrated *in vacuo*. The residue was immediately dissolved in CH₂Cl₂ (2 ml) and MeOH (0.2 ml). Camphorsulfonic acid (3.0 mg, 0.012 mmol) was added and the solution stirred at rt for 1.5 h. Solid K₂CO₃ (25 mg, 0.18 mmol) was added slowly during 10 min after which the mixture was poured into saturated aqueous NaHCO₃ (2 ml) and extracted with CH₂Cl₂ (3 x 5 ml). The combined organic extracts were dried (Na₂SO₄) and concentrated *in vacuo*, to give the crude diastereoisomeric acetals as a colourless oil which were used immediately in the next step.

A yellow solution of benzoyl chloride (15 μl , 0.129 mmol), DMAP (10 mg, 0.082 mmol) and *N,N*-diisopropylethylamine (80 μl , 0.459 mmol) in CH₂Cl₂ (0.5 ml) and 4Å MS was added to a stirred solution of the crude acetals in CH₂Cl₂ (1.5 ml). The reaction mixture was stirred for 1 h at rt before MeOH (0.5 ml) was added. After 10 min the mixture was poured into brine (3 ml) and extracted with CH₂Cl₂ (3 x 5 ml). The combined organic extracts were dried (Na₂SO₄) and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (5 g) eluting with 50% hexanes–Et₂O in hexanes to give 26 mg (29.1 μmol , 73% over 3 steps) of a mixture of the two diastereoisomers at C7 in the ratio 6:1 (determined by integration of signals derived from C12H [¹H NMR (400 MHz, C₆D₆): δ 4.24 (dd, major) and 4.17 (dd, minor)]. The mixture was purified by column chromatography on silica gel (5 g) eluting with 10–20% Et₂O in CH₂Cl₂ to give diastereoisomer **6.19** (16 mg, 17.9 μmol , 45%) along with an impure mixture of **6.19** and its C7-epimer (8 mg, 8.95 μmol , 23%). Data for benzoate **6.19**: [α]_D²⁰ +50.0 (*c* 0.55, CHCl₃); ν_{max} (CHCl₃)/cm^{–1} 3358, 2929, 2856, 1732, 1706, 1524, 1471, 1263, 1123, 1032, 836; δ_{H} (400 MHz, C₆D₆): 8.23 (2H, ddm, J 1.6, 8.3), 7.41 (2H, ddm, J 1.6, 8.1), 7.31 (1H, d, J 9.6, NH), 7.10–6.97 and 6.95–6.85 (6H, 2 m), 5.87 (1H, s, C7H), 5.86 (1H, t, J 9.7, C10H), 4.50 (1H, d, J 7.0, OCH_AH_BO), 4.44 (1H, d, J 7.0, OCH_AH_BO), 4.24 (1H, dd, J 6.6, 10.2, C12H), 3.95 (1H, dd, J 2.6, 11.7, C18H_AH_B), 3.86 (1H, dd, J 2.4,

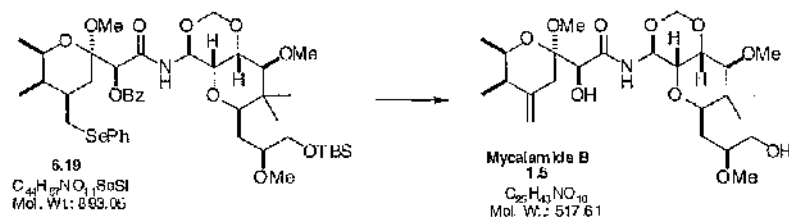
11.7, C18H_AH_B), 3.71 (1H, dd, *J* 6.7, 9.5, C11H), 3.49 (1H, dq, *J* 2.3, 6.7, C2H), 3.46 (1H, br d, *J* 8.8, C15H), 3.42–3.38 (1H, m, C17H), 3.32 (3H, s, OMe), 3.21 (3H, s, OMe), 3.05 (1H, d, *J* 10.1, C13H), 2.85 (3H, s, OMe), 2.78 (2H, dd, *J* 7.9, SeCH₂), 2.41–2.31 (1H, m, C4H), 2.20 (1H, dd, *J* 3.5, 8.1, C5H_AH_B), 2.09 (1H, ddd, *J* 0.8, 5.6, 10.6, C16H_AH_B), 1.69 (1H, t, *J* 13.0, C5H_AH_B), 1.66–1.57 (1H, m, C16H_AH_B), 1.52–1.48 (1H, m, C3H), 0.99 (3H, s, C14Me), 0.96 (9H, s, ^tBuSi), 0.89 (3H, s, C14Me), 0.80 (3H, d, *J* 6.6, C2Me), 0.77 (3H, d, *J* 7.1, C3Me), 0.101 (3H, s, MeSi), 0.091 (3H, s, MeSi); δ_C (100 MHz, C₆D₆): 165.3 (0), 164.0 (0), 132.0 (1), 131.5 (1), 129.7 (0), 129.0 (0), 128.9 (1, 2C), 128.0 (1, 2C), 127.4 (1, 2C), 125.6 (1, 2C), 98.0 (0, C6), 85.2 (2, OCH₂O), 78.0 (1, C13 or C17), 77.9 (1, C17 or C13), 75.1 (1, C15), 73.7 (1, C12), 72.9 (1, C7 or C10), 71.4 (1, C10 or C7), 70.3 (1, C11), 69.4 (1, C2), 61.0 (2, C18), 59.9 (3, OMe), 55.1 (3, OMe), 46.7 (3, OMe), 40.4 (0, C14), 34.2 (1, C3), 33.8 (1, C4), 30.8 (2, CH₂Se), 30.0 (2, C5), 28.5 (2, C16), 24.9 (3, 3C, ^tBuSi), 22.2 (3, C14Me), 17.3 (0, CSi), 16.8 (3, C2Me), 12.5 (3, C14Me), 3.4 (3, C3Me), –6.39 (3, MeSi), –6.49 (3, MeSi); *m/z* (FAB mode) 916 [(M+Na)⁺, 4%], 914 (2), 758 (1), 628 (1), 479 (4). Found: (M+Na)⁺, 916.3547. C₄₄H₆₇NO₁₁SeSiNa requires *M*, 916.3547.

17-epi-6.19



Acylidihydropyran **17-epi-6.18** (30.0 mg, 39.7 μ mol) was converted to **17-epi-6.19** (14 mg, 15.7 μ mol, 40%) by the procedure described above: $[\alpha]_D^{20}$ +61.4 (*c* 0.7, CHCl₃); ν_{max} (CHCl₃)/cm^{–1} 3359, 2929, 2856, 1732, 1706, 1523, 1471, 1263, 1124, 1030, 836; δ_H (400 MHz, C₆D₆): 8.21 (2H, ddm, *J* 1.5, 8.0), 7.45 (2H, ddm, *J* 1.5, 8.0), 7.36 (1H, d, *J* 9.6, NH), 7.05–6.88 (6H, m), 5.96 (1H, t, *J* 9.7, C10H), 5.91 (1H, s, C7H), 4.54 (1H, d, *J* 7.3, OCH_AH_BO), 4.52 (1H, d, *J* 7.5, OCH_AH_BO), 4.27 (1H, dd, *J* 6.9, 10.2, C12H), 3.73 (1H, dd, *J* 7.0, 9.6, C11H), 3.70 (1H, dd, *J* 9.4, 10.0, C15H), 3.67 (1H, dd, *J* 4.6, 9.9, C18H_AH_B), 3.62–3.57 (1H, m, C18H_AH_B), 3.58 (3H, s, OMe), 3.51 (1H, dq, *J* 2.3, 6.6, C2H), 3.51–3.43 (1H, m, C17H), 3.20 (3H, s, OMe), 3.01 (1H, *J* 10.3, C13H), 2.86 (1H, dd, *J* 7.1, 12.0, SeCH_AH_B), 2.86 (3H, s, OMe), 2.79 (1H, dd, *J* 8.6, 12.1, SeCH_AH_B), 2.44–2.35 (1H, m, C4H), 2.26 (1H, dd, *J* 3.5, 13.1, C5H_AH_B), 1.77 (1H, t, *J* 13.0, C5H_AH_B), 1.65 (1H, dd, *J* 10.2, 14.2, C16H_AH_B), 1.67–1.50 (1H, m, C3H), 1.46 (1H, br dd, *J* 9.3, 13.8, C16H_AH_B), 0.95 (9H, s, ^tBuSi), 0.92 (3H, s, C14Me), 0.88 (3H, s, C14Me), 0.81 (3H, d, *J* 6.4, C2Me), 0.80 (3H, d, *J* 7.1, C3Me), 0.063 (3H, s, MeSi), 0.061 (3H, s, MeSi); δ_C (100 MHz, C₆D₆): 165.4 (0), 146 (0), 132.0 (1), 131.7 (1, 2C), 129.4 (0), 128.9 (1, 2C), 128.1 (1, 2C), 127.3 (1, 2C), 125.8 (1), 124.5 (1), 98.0 (0, C6), 84.9 (2, OCH₂O), 77.8 (1, C13), 76.8 (1, C17), 74.6 (1, C15), 73.8 (1, C12), 72.9 (1, C10), 71.4 (1, C7), 70.4 (1, C11), 69.5 (1, C2), 63.9 (2, C18), 60.0 (3, OMe), 56.8 (3, OMe), 46.7 (3, OMe), 40.1 (0, C14), 34.1 (1, C4), 33.8 (1, C3), 32.2 (2, C16), 30.9 (2, CH₂Se), 30.3 (2, C5), 24.9 (3, 3C, ^tBuSi), 21.9 (3, C14Me), 17.3 (0, CSi), 16.8 (3, C2Me), 12.4 (3, C14Me), 3.3 (3, C3Me), –6.3 (3, MeSi), –6.4 (3, MeSi); *m/z* (FAB mode) 916 [(M+Na)⁺, 28%], 914 (16), 758 (6), 329 (24). Found: (M+Na)⁺, 916.3548. C₄₄H₆₇NO₁₁SeSiNa requires *M*, 916.3547.

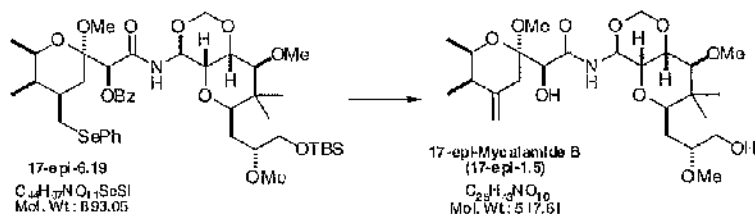
Mycalamide B (1.5)



Sodium periodate (30 mg, 0.14 mmol) was added in one portion to a solution of the diastereoisomerically pure selenide **6.19** (10 mg, 11.2 μ mol) in MeOH/H₂O/CH₂Cl₂ (3:1:1, 3.5 ml). After 30 min the mixture was diluted with Et₂O (10 ml) and Et₃N (0.5 ml) and washed with H₂O (2 x 5 ml), dried (Na₂SO₄) and concentrated *in vacuo* to give the selenoxide as a colourless oil which was dissolved in toluene (2 ml) whereupon Et₃N (2 ml, 14.3 μ mol) was added. After refluxing for 5 min, the reaction mixture was poured into saturated aqueous NaHCO₃ (5 ml) and extracted with Et₂O (2 x 10 ml). The organic extracts were dried (Na₂SO₄) and concentrated *in vacuo* to give a pale yellow oil which was dissolved in MeOH (3 ml) to which was added aqueous LiOH (0.3 ml, 1.0 M, 0.3 mmol). After 30 min at rt the mixture was concentrated, the residue was dissolved in Et₂O (5 ml), washed with H₂O (2 x 2 ml) and brine (2 ml), dried (Na₂SO₄), and concentrated *in vacuo* to give 18-*O*-TBS mycalamide B as a yellow oil which was used immediately in the next step.

TBAF (22 mg, 70 μ mol) was added to a solution of 18-*O*-TBS mycalamide B in THF (1 ml) and after 1 h at rt the reaction mixture was diluted with Et₂O (5 ml) and washed with saturated aqueous NaHCO₃ (2 ml). The aqueous phase was extracted with CH₂Cl₂ (2 x 5 ml) and the combined organic layers dried (Na₂SO₄) and concentrated *in vacuo* to give an oil which was purified by column chromatography on silica gel (1 g) eluting with hexanes:EtOAc:NEt₃ (100:0:1, 75:25:1, 50:50:1, 25:75:1, 0:100:1) to give mycalamide B (**1.5**) (4.5 mg, 8.69 μ mol, 78% over 4 steps): ν_{\max} (CHCl₃)/cm⁻¹ 3359, 2971, 2933, 1686, 1522, 1468, 1382, 1193, 1109, 1075, 1032, 959, 879, 789; δ_{H} (400 MHz, CDCl₃): 7.54 (1H, d, *J* 9.6, NH), 5.83 (1H, t, *J* 9.6, C10H), 5.14 (1H, d, *J* 7.0, OCH_AH_BO), 4.88 (1H, d, *J* 6.7, OCH_AH_BO), 4.88 (1H, br s, =CH_AH_B), 4.75 (1H, br s, =CH_AH_B), 4.31 (1H, d, *J* 2.0, C7H), 4.24 (1H, dd, *J* 6.8, 10.2, C12H), 4.06 (1H, dq, *J* 2.8, 6.5, C2H), 3.90 (1H, d, *J* 2.1, C7OH), 3.81 (1H, dd, *J* 6.8, 9.6, C11H), 3.72–3.65 (1H, m, C18H_AH_B), 3.58 (3H, s, OMe), 3.54–3.48 (1H, m, C18H_AH_B), 3.46 (1H, d, *J* 10.4, C13H), 3.48–3.42 (1H, m hidden, C15H), 3.32 (3H, s, OMe), 3.27 (3H, s, OMe), 3.25–3.18 (1H, m, C17H), 2.39 (1H, d, *J* 14.0, C5H_AH_B), 2.30 (1H, dq, *J* 2.8, 7.1, C3H), 2.26 (1H, dm, *J* 13.9, C5H_AH_B), 1.60–1.54 (2H, m, C16H₂), 1.23 (3H, d, *J* 6.6, C2Me), 1.04 (3H, d, *J* 7.2, C3Me), 1.01 (3H, s, C14Me), 0.89 (3H, s, C14Me); δ_{C} (400 MHz, C₆D₆): 7.58 (1H, d, *J* 9.8, NH), 5.83 (1H, t, *J* 9.9, C10H), 4.71 (1H, t, *J* 1.8, =CH_AH_B), 4.66 (1H, t, *J* 1.9, =CH_AH_B), 4.56 (1H, d, *J* 7.0, OCH_AH_BO), 4.53 (1H, d, *J* 6.9, OCH_AH_BO), 4.24 (1H, dd, *J* 7.0, 10.6, C12H), 4.16 (1H, s, C7H), 4.07 (1H, br s, C7OH), 3.85–3.77 (1H, m, C18H_AH_B), 3.80 (1H, dq, *J* 1.8, 6.6, C2H), 3.74–3.68 (1H, m, C18H_AH_B), 3.69 (1H, dd, *J* 7.0, 10.0, C11H), 3.40 (1H, dd, *J* 5.6, 6.1, C15H), 3.33–3.28 (1H, m, C17H), 3.22 (3H, s, C13OMe), 3.15 (3H, s, C6OMe), 3.03 (3H, s, C17OMe), 2.94 (1H, d, *J* 10.5, C13-H), 2.60 (1H, d, *J* 14.0, C5-H_AH_B), 2.40 (1H, dt, *J* 1.8, 14.0, C5H_AH_B), 2.33 (1H, br s, C18OH), 1.86 (1H, dq, *J* 1.7, 7.0, C3H), 1.59–1.55 (2H, m, C16H₂), 0.92 (3H, d, *J* 7.0, C3Me), 0.81 (3H, d collapsed by C14Me, *J* 6.6, C2Me), 0.80 (3H, s, C14Me), 0.76 (3H, s, C14Me); δ_{C} (100 MHz, C₆D₆): 171.1 (O, C8), 144.6 (O, C4), 109.6 (2, =CH₂), 99.2 (O, C6), 85.1 (2, OCH₂O), 77.7 (1, C13 or C17), 77.5 (1, C17 or C13), 74.4 (1, C15), 73.9 (1, C12), 72.9 (1, C10), 70.9 (1, C7 or C11), 70.7 (1, C11 or C7), 68.1 (1, C2), 62.6 (2, C18), 60.0 (3, C13OMe), 55.2 (3, C17OMe), 47.0 (3, C6OMe), 40.4 (1, C3), 40.3 (O, C14), 32.9 (1, C5), 29.3 (2, C16), 21.5 (3, C14Me_{eq}), 16.5 (3, C2Me_{ax}), 11.9 (3, C14Me), 11.0 (3, C3Me); *m/z* (FAB modc) 540 [(M+Na)⁺, 100%], 507 (20), 486 (25), 176 (32). Found: (M+Na)⁺, 540.2790. C₂₅H₄₃NO₁₀-Na requires *M*, 540.2785.

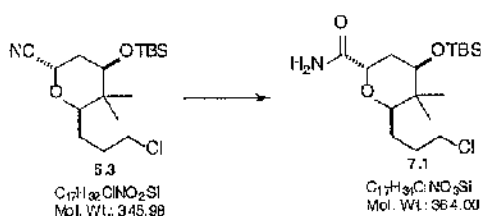
17-*epi*-Mycalamide B



Selenide **17-*epi*-6.19** (14 mg, 15.7 μ mol) gave 17-*epi*-mycalamide B (**17-*epi*-1.5**) (6.3 mg, 12.2 μ mol, 78% over 4 steps) by the procedure described above: ν_{\max} (CHCl₃)/cm⁻¹ 3356, 2971, 2933, 1686, 1524, 1468, 1382, 1194, 1109, 1074, 1033, 959, 878, 790; δ_H (400 MHz, C₆D₆): 7.48 (1H, d, *J* 9.9, NH), 5.94 (1H, t, *J* 9.9, C10H), 4.75–4.70 (2H, m, =CH₂), 4.57 (1H, d, *J* 6.9, OCH_AH_BO), 4.54 (1H, d, *J* 6.9, OCH_AH_BO), 4.23 (1H, dd, *J* 6.9, 10.2, C12H), 4.17 (2H, s, C7H and C7OH), 3.82 (1H, dq, *J* 2.6, 6.6, C2H), 3.65 (1H, dd, *J* 7.1, 9.7, C11H), 3.61–3.55 (2H, m, C18H₂), 3.51 (1H, d, *J* 9.3, C15H), 3.32 (3H, s, C13OMe), 3.27–3.18 (1H, m, C17H), 3.21 (3H, s, C6OMe), 3.06 (3H, s, C17OMe), 2.96 (1H, d, *J* 10.4, C13H), 2.60 (1H, d, *J* 13.9, C5H_AH_B), 2.42 (1H, br d, *J* 13.9, C5H_AH_B), 1.88 (1H, dq, *J* 2.6, 7.1, C3H), 1.65 (1H, dd, *J* 8.2, 14.8, C16H_AH_B), 1.50 (1H, br s, C18OH), 1.27 (1H, ddd, *J* 2.8, 10.0, 14.3, C16H_AH_B), 0.90 (3H, d, *J* 7.1, C3Me), 0.83 (3H, s, C14Me), 0.81 (3H, d, *J* 6.6, C2Me), 0.77 (3H, s, C14Me); δ_C (100 MHz, C₆D₆): 171.1 (0, C8), 145.0 (0, C4), 109.4 (2, =CH₂), 99.1 (0, C6), 85.0 (2, OCH₂O), 78.3 (1, C17), 77.8 (1, C13), 75.9 (1, C15), 73.8 (1, C12), 72.8 (1, C10), 71.1 (1, C7), 70.1 (1, C11), 68.0 (1, C2), 62.6 (2, C18), 60.0 (3, C13OMe), 55.6 (3, C17OMe), 47.1 (3, C6OMe), 40.3 (1, C3), 40.1 (0, C14), 33.0 (1, C5), 31.5 (2, C16), 21.7 (3, C14Me), 16.5 (3, C2Me), 12.1 (3, C14Me), 11.1 (3, C3Me); *m/z* (FAB mode) 540 [(M+Na)⁺, 100%], 508 (20), 486 (25). Found: (M+Na)⁺, 540.2789. C₂₅H₄₃NO₁₀Na requires *M*, 540.2785.

10.5 Synthesis of analogues of pederin

(2*S*,4*R*,6*R*)-4-(*tert*-Butyldimethylsilyloxy)-6-(3-chloropropyl)-5,5-dimethyl-tetrahydro-pyran-2-carboxamide (**7.1**).



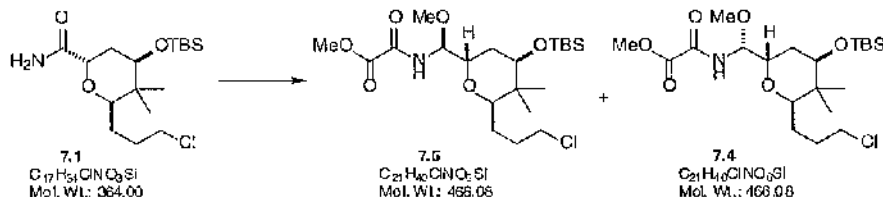
To a solution of nitrile **5.3** (14.3 g, 41.3 mmol) in EtOH (100 ml) and CH₂Cl₂ (50 ml) at 0°C, was added a solution of K₂CO₃ (107.3 g, 776 mmol) in water (50 ml) followed by H₂O₂ (148 ml, 30% aqueous solution, 930 mmol) and *n*-tetrabutylammonium hydrogen sulfate (2.80 g, 8.3 mmol) causing strong gas evolution. The reaction mixture was stirred at rt (using a water bath) for 7 days while H₂O₂ (50 ml, 30% aqueous solution, 310 mmol) was added every 24 h. Saturated aqueous Na₂S₂O₃ (150 ml) was added dropwise until effervescence ceased. The phases were separated and the aqueous phase was extracted with CH₂Cl₂ (3 x 150 ml). The combined organic extracts were dried (MgSO₄), and concentrated *in vacuo*. The residue was purified by column chromatography (SiO₂, hexanes/Et₂O 0-50%) to give amide **7.1** (9.73 g, 26.7 mmol, 65%) as a white solid and recovered nitrile **5.3** (2.16 g, 6.25 mmol, 15 %) : mp 90-92°C (hexanes); $[\alpha]_D^{23}$ +19.4 (c 0.9, CHCl₃); ν_{\max} film/cm⁻¹ 3482, 3313, 3204, 2956, 2857, 1694, 1586, 1471, 1388, 1256, 1086;

δ_{H} (400 MHz, CDCl_3): 6.35 (1H, br s, NH_AH_B), 5.49 (1 H, br s, NH_AH_B), 4.35 (1H, t, J 4.9, C11-H), 3.59 (1H, ddd, J 10.7, 6.6, 3.0, C18 H_AH_B), 3.55 (1H, ddd, J 10.7, 6.5, 2.8, J 10.7, 6.5, 2.8, C18 H_AH_B), 3.45 (1H, dd, J 8.9, 4.0, C13-H), 3.22 (1H, dd, J 10.7, 1.8, C15-H), 2.22 (1H, dt, J 13.4, 4.4, C12- H_AH_B), 2.10-1.96 (1H, m, C17- H_AH_B), 1.90-1.60 (4H, m, C12- H_AH_B , C16- H_2 , C17- H_AH_B), 0.92 (3H, s, C14-Me), 0.91 (9H, s, $t\text{BuSi}$), 0.89 (3H, s, C14-Me), 0.11 (3H s, Si-Me), 0.06 (3H, s, Si-Me); δ_{C} (100 MHz, CDCl_3): 174.3 (0, C10), 81.0 (1, C15), 72.8 (1, C13), 70.8 (1, C11), 44.9 (2, C18), 38.3 (0, C14), 30.3 (2, 2C, C12 and C17), 26.2 (2, C16), 25.8 (3, 3C, $t\text{BuSi}$), 24.3 (3, C14-Me), 18.0 (0, C-Si), 15.7 (3, C14-Me), -4.2 (3, Me-Si), -5.0 (3, Me-Si); m/z (CI, Isobutane) 366 (35), 364 [(M+H) $^+$, 100%], 308 (7), 306 (21), 234 (30), 232 (100), 174 (20); Found: (M+H) $^+$, 364.2073. $\text{C}_{17}\text{H}_{35}\text{O}_3\text{NSiCl}$ requires M , 364.2075; Found: C, 56.04; H, 9.39; N, 3.84. $\text{C}_{17}\text{H}_{34}\text{ClNO}_3\text{Si}$ requires C, 56.09; H, 9.41; N, 3.85.

N-{[(2*S*,4*R*,6*R*)-4-(*tert*-Butyldimethylsilyloxy)-6-(3-chloropropyl)-5,5-dimethyl-tetrahydro-pyran-2-yl]-(*S*)-methoxy-methyl}-oxalamic acid methyl ester (7.5)

and

N-{[(2*S*,4*R*,6*R*)-4-(*tert*-Butyldimethylsilyloxy)-6-(3-chloropropyl)-5,5-dimethyl-tetrahydro-pyran-2-yl]-(*R*)-methoxy-methyl}-oxalamic acid methyl ester (7.4)

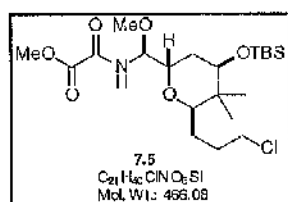


To a solution of amide **7.1** (1.06 g, 2.9 mmol) in CH_2Cl_2 (50 ml) was added in one portion freshly purchased Me_3OBF_4 (1.76 g, 11.9 mmol, 4.1 eq). After 4.5 h at rt, the mixture was poured onto saturated aqueous NaHCO_3 (50 ml) and extracted with CH_2Cl_2 (3 x 25 ml), dried (MgSO_4) and concentrated *in vacuo* to give **7.2** as a colourless oil which was used immediately in the following step.

To a solution of crude methyl imidate **7.2** in CH_2Cl_2 (50 ml) at 0 °C was added pyridine (1.1 ml, 13.6 mmol) followed immediately by methyl oxalyl chloride (350 μl , 3.8 mmol). After 10 min at 0 °C, the mixture was poured into saturated aqueous NaHCO_3 (20 ml) and extracted quickly with CH_2Cl_2 (3 x 40 ml), dried (MgSO_4) and concentrated *in vacuo* to give **7.3** as a colourless oil which was used immediately in the next step.

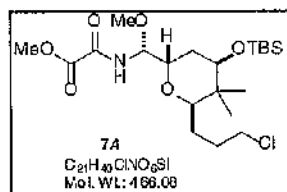
To a solution of crude *N*-acylimidate **7.3** in toluene (40 ml) at rt was added $\text{RhCl}[\text{Ph}_3\text{P}]_3$ (135 mg, 0.15 mmol). The mixture was cooled to -75 °C and freshly prepared catecholborane¹³⁵ (5.8 ml, 2.9 mmol, 0.5 M solution in THF) was added. The reaction mixture was stirred at -70 °C for 2 h and poured into saturated aqueous NaHCO_3 (20 ml) and extracted with CH_2Cl_2 (3 x 40 ml). The combined organic extracts were dried (MgSO_4), and concentrated *in vacuo* to give a yellow oil which was purified by column chromatography (SiO_2 , 10–30% EtOAc in hexanes) to give **7.5** (620 mg, 1.33 mmol, 46%) as a colourless oil which crystallised on standing and **7.4** (112 mg, 0.24 mmol, 8.3 %) as a colourless oil (dr = 5.5:1).

N-{[(2*S*,4*R*,6*R*)-4-(*tert*-Butyldimethylsilyloxy)-6-(3-chloropropyl)-5,5-dimethyl-tetrahydro-pyran-2-yl]-(*S*)-methoxy-methyl}-oxalamic acid methyl ester (7.5)



mp 40-42°C (hexanes); $[\alpha]_D^{20} +21.4$ (c 1.0, CHCl₃); ν_{\max} film/cm⁻¹ 3403, 3359, 2953, 2857, 1713, 1518, 1471, 1361, 1295, 1210; δ_H (400 MHz, CDCl₃): 7.48 (1H, d, *J* 9.7, NH), 5.21 (1H, dd, *J* 9.8, 6.7, C10-H), 3.93 (3H, s, OMe), 3.84 (1H, dt, *J* 7.1, 5.5, C11-H), 3.54 (1H, dd, *J* 8.3, 4.0, C13-H), 3.48 (2H, t, *J* 6.6, C18-H₂), 3.40 (3H, s, OMe), 3.17 (1H, dd, *J* 11.0, 1.4, C15-H), 1.91-1.79 (3H, m), 1.70-1.48 (3H, m), 0.92 (3H, s, C14-Me), 0.90 (9H, s, ^{*t*}BuSi), 0.85 (3H, s, C14-Me), 0.055 (3H, s, Si-Me), 0.049 (3H, s, Si-Me); δ_C (100 MHz, CDCl₃): 160.5 (0), 157.2 (0), 80.9 (1, C10), 79.8 (1, C15), 72.6 (1, C13), 70.0 (1, br signal, C11), 56.8 (3, OMe), 53.8 (3, OMe), 45.1 (2, C18), 38.4 (0, C14), 30.3 (2, C12 or C16 or C17), 29.9 (2, C12 or C16 or C17), 26.0 (2, C12 or C16 or C17), 25.7 (3, 3C, ^{*t*}BuSi), 24.5 (3, C14-Me), 18.0 (0, C-Si), 16.5 (3, br signal, C14-Me), -4.4 (3, Me-Si), -5.0 (3, Me-Si); *m/z* (CI, Isobutane) 366 (35), 364 [(M+H)⁺, 100%], 308 (7), 306 (21), 234 (30), 232 (100), 174 (20); *m/z* (FAB, NaI) 490 (40), 488 [(M+Na)⁺, 100%], 304 (15), 302 (45); Found: (M+Na)⁺, 488.2212. C₂₁H₄₀O₆NSiClNa requires *M*, 488.2211.

N-{[(2*S*,4*R*,6*R*)-4-(*tert*-Butyldimethylsilyloxy)-6-(3-chloropropyl)-5,5-dimethyl-tetrahydro-pyran-2-yl]-(*R*)-methoxy-methyl}-oxalamic acid methyl ester (7.4)

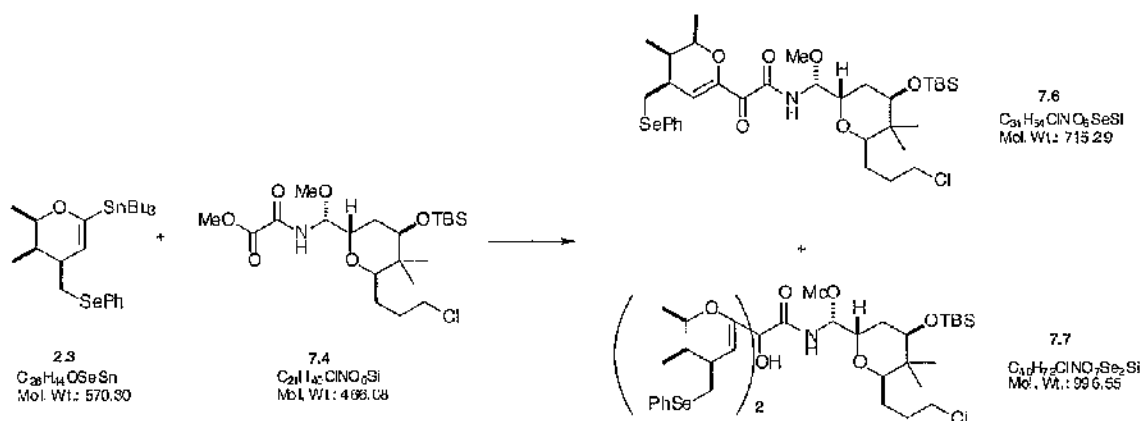


$[\alpha]_D^{17} +13.5$ (c 0.5, CHCl₃); ν_{\max} film/cm⁻¹ 3404, 3358, 2954, 2857, 1713, 1518, 1471, 1361, 1295, 1210; δ_H (400 MHz, CDCl₃): 7.84 (1H, d, *J* 9.7, NH), 5.10 (1H, dd, *J* 9.9, 3.4, C10-H), 3.93 (3H, s, OMe), 3.87-3.82 (1H, m (5 lines), C11-H), 3.68 (1H, dd, *J* 6.0, 3.6, C13-H or C15-H), 3.58 (2H, dd, *J* 6.6, 6.2, C18-H₂), 3.50 (1H, dd, *J* 11.7, 2.4, C15-H or C13-H), 3.41 (3H, s, OMe), 2.14-1.93 (2H, m), 1.82-1.73 (1H, m), 1.63-1.54 (3H, m), 1.02 (3H, s, C14-Me), 0.90 (9H, s, ^{*t*}BuSi), 0.87 (3H, s, C14-Me), 0.06 (3H, s, Si-Me), 0.04 (3H, s, Si-Me); δ_C (100 MHz, CDCl₃): 160.9 (0), 156.8 (0), 82.8 (1, C10), 81.1 (1, C13 or C15), 73.4 (1, C15 or C13), 68.7 (1, C11), 57.4 (3, OMe), 54.2 (OMe), 45.4 (2, C18), 38.3 (0, C14), 31.4 (2, C12 or C16 or C17), 30.2 (2, C12 or C16 or C17), 30.0 (2, C12 or C16 or C17), 26.2 (3, 3C, ^{*t*}BuSi), 25.7 (3, C14-Me), 19.6 (0, br signal, C14-Me), 18.3 (0, C-Si), -4.1 (3, Me-Si), -4.7 (3, Me-Si); *m/z* (FAB, NaI) 490 (40), 488 [(M+Na)⁺, 100%]; Found: (M+Na)⁺, 488.2210. C₂₁H₄₀O₆NSiClNa requires *M*, 488.2211.

N-[(2*S*,4*R*,6*R*)-4-(*tert*-Butyldimethylsilyloxy)-6-(3-chloropropyl)-5,5-dimethyl-tetrahydro-pyran-2-yl]-(*R*)-methoxy-methyl]-2-((4*S*,5*R*,6*R*)-5,6-dimethyl-4-phenylselanylmethyl-5,6-dihydro-4*H*-pyran-2-yl)-2-oxo-acetamide (7.6)

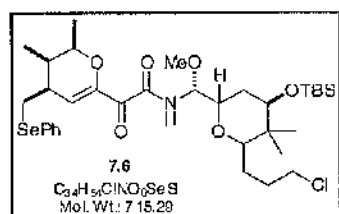
and

N-[(2*S*,4*R*,6*R*)-4-(*tert*-Butyldimethylsilyloxy)-6-(3-chloropropyl)-5,5-dimethyl-tetrahydro-pyran-2-yl]-(*R*)-methoxy-methyl]-2,2-bis-((4*S*,5*R*,6*R*)-5,6-dimethyl-4-phenylselanylmethyl-5,6-dihydro-4*H*-pyran-2-yl)-2-hydroxy-acetamide (7.7)



To a solution of stannane **2.3** (257 mg, 0.45 mmol) in THF (3 ml) at -90°C was added dropwise *n*BuLi (200 μl , 0.454 mmol, 2.27 M solution in hexanes) and the bright yellow solution stirred while maintaining the temperature between -85 and -90°C for 15 min. Formation of the lithiated dihydropyran was checked by TLC (Al₂O₃, hexanes). TMEDA (68 μl , 0.45 mmol) was added and after 10 min at -90°C , a solution of ester **7.4** (63 mg, 0.135 mmol) in THF (1.5 ml) was quickly added using a wide bore cannula. The light yellow solution was allowed to gradually warm up to -40°C over 3 h and then poured into brine (5 ml) and extracted with CH₂Cl₂ (3 x 10 ml). The combined extracts were dried (Na₂SO₄) and concentrated *in vacuo* to give a yellow oil which was purified by chromatography (SiO₂, PhMe and then 0-30% Et₂O in hexanes) to give coupling product **7.6** (45.0 mg, 0.063 mmol, 45% based on the right half fragment **7.4**) as a colourless oil along with byproduct **7.7** (46.0 mg, 0.046 mmol, 34%) as a white powder.

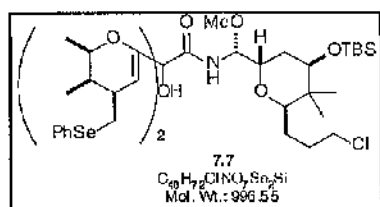
N-[(2*S*,4*R*,6*R*)-4-(*tert*-Butyldimethylsilyloxy)-6-(3-chloropropyl)-5,5-dimethyl-tetrahydro-pyran-2-yl]-(*R*)-methoxy-methyl]-2-((4*S*,5*R*,6*R*)-5,6-dimethyl-4-phenylselanylmethyl-5,6-dihydro-4*H*-pyran-2-yl)-2-oxo-acetamide (7.6)



$[\alpha]_{\text{D}}^{20} -18.4$ (c 0.8, CHCl₃); ν_{max} film/cm⁻¹ 3394, 3311, 2932, 2857, 1667, 1580, 1500, 1381, 1253, 1074, 878, 837, 776, 738, 584; δ_{H} (400 MHz, CDCl₃): 7.70 (1H, d, *J* 9.8, NH), 7.54-7.40 (2H, m, Harom), 7.30-7.25 (3H, m, Harom), 7.04 (1H, t, *J* 1.9, C5-H), 5.08 (1H, dd, *J* 6.2, 3.6, C10-H), 4.10 (1H, dq, *J* 6.5, 1.3, C2-H), 3.85-3.80 (1H, m, 5 lignes, C11-H), 3.68 (1H, dd, *J* 6.1, 3.6, C13-H), 3.64-3.57 (2H, m, C18-H₂), 3.14 (1H, dd, *J* 9.6, 2.4, C15-H), 3.40 (3H, s, OMe), 2.99 (1H, d, *J* 12.1, Se-CH₂H_B), 2.94 (1H, d, *J* 12.1, Se-

CH_AH_B), 2.90-2.83 (1H, m, C4-H), 2.12-1.90 and 1.79-1.43 (7H, 2 x m, C3-H, C12-H₂, C16-H₂ and C17-H₂), 1.38 (3H, d, *J* 6.5, C2-Me), 1.01 (3H, s, C14-Me), 0.90 (9H, s, ^tBu-Si), 0.88 (3H, s, C14-Me), 0.85 (3H, d, *J* 7.0, C3-Me), 0.06 (3H, s, Me-Si), 0.04 (3H, s, Me-Si); δ_C (100 MHz, CDCl₃): 180.5 (O), 160.8 (O), 148.2 (O, C6), 133.1 (1, 2C, Carom), 129.2 (1, 2C, Carom), 129.2 (O, Carom), 127.3 (1, Carom), 124.2 (1, C5), 81.9 (1, C10), 80.5 (1, C15), 76.7 (1, C2), 73.1 (1, C13), 68.5 (1, C11), 56.9 (3, OMe), 45.4 (2, C18), 39.0 (1, C4), 37.9 (O, C14), 33.2 (1, C3), 31.1 (2, C12 or C16 or C17), 29.5 (2, Se-CH₂), 29.4 (2, C12 or C16 or C17), 25.8 (3, 3C, ^tBu-Si), 25.5 (3, C14-Me), 25.2 (2, C12 or C16 or C17), 19.2 (3, C14-Me), 18.2 (3, C2-Me), 17.8 (O, C-Si), 5.9 (3, C3-Me), -4.4 (3, Me-Si), -5.0 (3, Me-Si); *m/z* (FAB, NaI) 743 (5), 742 (10), 741 (20), 740 (50), 739 (45), 738 [(M+Na)⁺, 100%], 736 (50), 737 (25), 736 (55), 735 (20), 734 (15), 733 (5), 584 (4), 583 (6), 582 (18), 581 (16), 580 (32), 579 (2), 578 (2); Found : (M+Na)⁺ 738.2465. C₃₄H₅₄O₆SeSiClNa requires *M*, 738.2473.

N-{[(2*S*,4*R*,6*R*)-4-(tert-Butyldimethylsilyloxy)-6-(3-chloropropyl)-5,5-dimethyl-tetrahydro-pyran-2-yl]-(*R*)-methoxy-methyl}-2,2-bis-[(4*S*,5*R*,6*R*)-5,6-dimethyl-4-phenylselanylmethyl-5,6-dihydro-4*H*-pyran-2-yl]-2-hydroxy-acetamide (7.7)

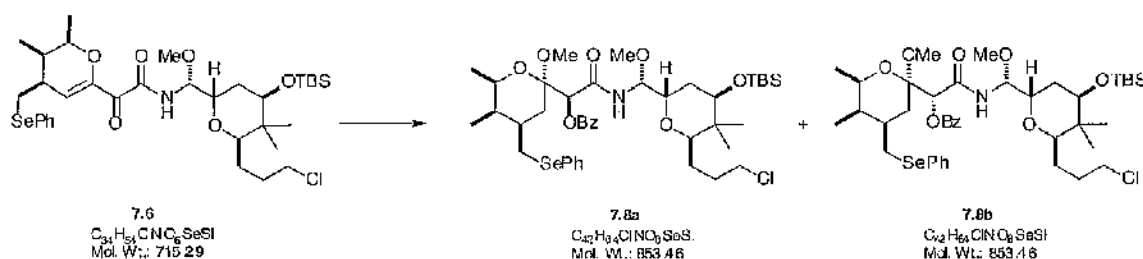


mp 38-40°C (hexanes); $[\alpha]_D^{21} +35.9$ (c 0.3, CHCl₃); ν_{\max} film/cm⁻¹ 3393, 2931, 1686, 1514, 1471, 1381, 1253, 1100, 879, 837, 776, 737, 584; δ_H (400 MHz, CDCl₃): 7.50-7.46 (4H, m, Harom), 7.30-7.23 (6H, m, Harom), 7.06 (1H, d, *J* 9.7, NH), 5.27 (1H, dd, *J* 9.7, 6.2, C10-H), 5.09 (1H, t, *J* 1.5, C5-H), 4.99 (1H, t, *J* 1.8, C5'-H), 4.50 (1H, s, C7-H), 4.02 (1H, dq, *J* 6.5, 1.3, C2-H), 3.97 (1H, dq, *J* 6.6, 1.3, C2'-H), 3.70-3.64 (2H, m, C11-H and C13-H), 3.60-3.46 (2H, m, C18-H₂), 3.40 (3H, s, OMe), 3.31 (1H, dd, *J* 7.9, 4.5, C15-H), 2.93-2.79 (4H, m, Se-CH₂ and Se'-CH₂), 2.75-2.68 (1H, m, C4-H), 2.68-2.60 (1H, m, C4'-H), 2.07-1.95 and 1.95-1.85 and 1.78-1.52 (8H, 3 x m, C3-H, C3'-H, C12-H₂, C16-H₂ and C17-H₂), 1.26 (3H, d, *J* 6.5, C2-Me), 1.24 (3H, d, *J* 6.5, C2'-Me), 0.90 (3H, s, C14-Me), 0.87 (9H, s, ^tBu-Si), 0.834 (3H, s, C14-Me), 0.831 (3H, d, *J* 6.8, C3-Me), 0.79 (3H, d, *J* 6.9, C3'-Me), 0.05 (3H, s, Me-Si), -0.04 (3H, s, Me-Si); δ_C (100 MHz, CDCl₃): 171.1 (O), 151.4 (O, C6), 150.4 (O, C6'), 132.7 (1, 2C, Carom), 132.6 (1, 2C, Carom), 129.9 (O, Carom), 129.1 (O, Carom), 129.1 (1, 2C, Carom), 127.0 (1, 2C, Carom), 126.9 (1, 2C, Carom), 101.2 (1, 2C, C5 and C5'), 81.7 (1, C10), 79.2 (1, C15), 77.0 (1, C7), 77.0 (1, C2), 76.6 (1, C2'), 72.5 (1, C11 or C13), 72.2 (1, C11 or C13), 56.3 (3, OMe), 45.2 (2, C18), 38.8 (O, C14), 37.5 (1, C4), 37.4 (1, C4'), 33.9 (1, C3), 33.6 (1, C3'), 30.9 (2, C12 or C16 or C17), 30.7 (2, 2C, Se-CH₂ and Se'-CH₂), 30.1 (2, C12 or C16 or C17), 26.3 (2, C12 or C16 or C17), 25.8 (3, 3C, ^tBu-Si), 23.8 (3, C14-Me), 18.3 (3, C2-Me), 18.2 (3, C2'-Me), 18.0 (O, C-Si), 14.5 (3, br s, C14-Me), 5.7 (3, C3-Me), 5.4 (3, C3'-Me), -4.1 (3, Me-Si), -5.1 (3, Me-Si); *m/z* (FAB, NaI) 1026 (5), 1025 (7), 1024 (20), 1023 (30), 1022 (60), 1021 (55), 1020 [(M+Na)⁺, 100%], 1019 (55), 1018 (90), 1017 (45), 1016 (47), 1015 (20), 1014 (20), 1013 (5), 1012 (5), 866 (4), 865 (6), 864 (13), 863 (12), 862 (20), 861 (7), 860 (12), 859 (5), 858 (5); Found : (M+Na)⁺ 1020.2986. C₄₈H₇₂O₇N⁸⁰Se₂Si³⁵ClNa requires *M*, 1020.2994 and C₄₈H₇₂O₇N⁷⁸Se⁸⁰SeSi³⁷ClNa requires *M*, 1020.2973.

(*S*)-Benzoic acid ([[(2*S*,4*R*,6*R*)-4-(*tert*-butyldimethylsilanyloxy)-6-(3-chloropropyl)-5,5-dimethyl-tetrahydro-pyran-2-yl]-(*R*)-methoxy-methyl]-carbamoyl)-((2*R*,4*R*,5*R*,6*R*)-2-methoxy-5,6-dimethyl-4-phenylselanylmethyl-tetrahydro-pyran-2-yl)-methyl ester (**7.8a**)

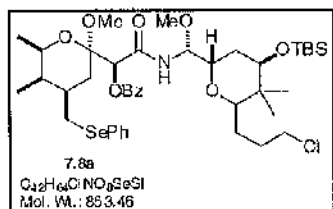
and

(*R*)-Benzoic acid ([[(2*S*,4*R*,6*R*)-4-(*tert*-butyldimethylsilanyloxy)-6-(3-chloropropyl)-5,5-dimethyl-tetrahydro-pyran-2-yl]-(*R*)-methoxy-methyl]-carbamoyl)-((2*R*,4*R*,5*R*,6*R*)-2-methoxy-5,6-dimethyl-4-phenylselanylmethyl-tetrahydro-pyran-2-yl)-methyl ester (**7.8b**)



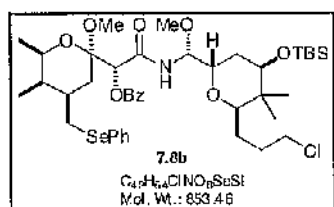
To a solution of acyl dihydropyran **7.6** (35 mg, 48.9 μ mol) in THF (3 ml) at -90°C was added $\text{LiBH}(\text{s-Bu})_3$ (0.125 ml, 1.0 M solution in THF, 0.125 mmol) over 3 min. After 10 min maintaining the temperature between -85 and -90°C the mixture was treated with brine (1 ml) and extracted with CH_2Cl_2 (3 x 5 ml). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo* to give the corresponding alcohols as a pale yellow oil. The crude alcohols were immediately dissolved in CH_2Cl_2 (2.5 ml) and MeOH (0.25 ml). Camphorsulfonic acid (4.0 mg, 17.0 μ mol) was added and the solution stirred at rt. After 3 h at rt solid K_2CO_3 (35 mg, 0.24 mmol) was added slowly over 10 min. The reaction mixture was stirred for another 20 min and then poured onto saturated aqueous NaHCO_3 (2 ml) and extracted with CH_2Cl_2 (3 x 5 ml). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*, to give the diastereoisomeric acetals as a pale yellow oil which were used immediately in the next step. ^1H NMR (400 Mhz, CDCl_3) spectroscopy confirmed complete addition of methanol on the dihydropyran ring and the ratio of the C7-diastereomers (c.a. dr = 3:2) was determined by integration of the N-H (1H, d) at $\delta = 7.70$ ppm (major) and $\delta = 7.59$ ppm (minor). A solution of benzoyl chloride (200 μ l, 1.71 mmol), DMAP (125 mg, 1.02 mmol), DIPEA (1 ml, 5.70 mmol) and 4 \AA MS (5) was prepared in CH_2Cl_2 (19 ml). To the crude acetal alcohols was added 2 ml of the above solution and the reaction mixture was stirred at rt for 15 h before MeOH was added (1 ml). After 20 min the mixture was poured into brine (2 ml) and extracted with CH_2Cl_2 (3 x 5 ml). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2 , PhMe and then 0–40% Et_2O in hexanes) to give a mixture of diastereoisomers **7.8a**:**7.8b** (30 mg, 0.035 mmol, 72%). ^1H NMR (400 MHz, CDCl_3) spectroscopy confirmed the ratio of the C7-diastereomers to be dr = 2:1 which was determined by integration of the C7-H (1H, s) at $\delta = 5.73$ ppm (minor) and $\delta = 5.46$ ppm (major). Benzoates **7.8a** and **7.8b** were separated and purified by HPLC using a HiCHROM column (NC100-7C18-250 SP1, Nucleosil 100-7C18, 25 cm-10 mm) eluting with MeCN. Retention time were recorded to be 16.3–18.4 min (major) and 18.4–20.6 min (minor) to afford benzoate **7.8a** (10.6 mg, 12.42 μ mol, 25%) as a colourless oil, and benzoate **7.8b** (6.7 mg, 7.85 μ mol, 16%) as a white solid.

(*S*)-Benzoic acid ([[(2*S*,4*R*,6*R*)-4-(*tert*-butyldimethylsilyloxy)-6-(3-chloropropyl)-5,5-dimethyl-tetrahydro-pyran-2-yl]-(*R*)-methoxy-methyl]-carbamoyl)-((2*R*,4*R*,5*R*,6*R*)-2-methoxy-5,6-dimethyl-4-phenylsilylmethyl-tetrahydro-pyran-2-yl)-methyl ester (7.8a)



$[\alpha]_D^{20} +53.0$ (c 0.4, CHCl₃); ν_{\max} film/cm⁻¹ 3305, 2955, 2927, 2854, 1720, 1671, 1548, 1455, 1381, 1271, 1095; δ_H (400 MHz, CDCl₃): 8.10 (2H, dd, *J* 8.3, 1.4, Harom), 7.59 (1H, tt, *J* 7.5, 1.2, Harom), 7.54-7.49 (2H, m, Harom), 7.49-7.44 (2H, m, Harom), 7.30-7.24 (4H, m, 3 x Harom and NH), 5.46 (1H, s, C7-H), 5.11 (1H, dd, *J* 9.7, 4.3, C10-H), 3.98 (1H, dq, *J* 6.6, 2.1, C2-H), 3.80 (1H, app q, *J* 4.1, C11-H), 3.63 (1H, dd, *J* 5.2, 3.8, C13-H), 3.63-3.50 (2H, C18-H₂), 3.42 (3H, s, OMe), 3.39 (1H, dd, *J* 11.5, 2.3, C15-H), 3.21 (3H, s, OMe), 2.94 (1H, dd, *J* 12.0, 6.4, Se-CH_AH_B), 2.84 (1H, dd, *J* 12.0, 9.4, Se-CH_AH_B), 2.40-2.34 (1H, m, C4-H), 2.20-2.09 (1H, m), 2.09-2.95 (3H, m), 1.90-1.80 (1H, m, C3-H), 1.80-1.68 (2H, m), 1.65-1.45 (2H, m), 1.21 (3H, d, *J* 6.6, C2-Me), 1.01 (3H, s, C14-Me), 0.90 (9H, s, ^tBu-Si), 0.88 (3H, s, C14-Me), 0.79 (3H, d, *J* 7.1, C3-Me), 0.04 (3H, s, Si-Me), 0.02 (3H, s, Si-Me); δ_C (100 MHz, CDCl₃): 167.3 (O), 165.4 (O), 133.4 (1, Carom), 132.6 (1, 2C, Carom), 130.3 (O, Carom), 130.1 (1, 2C, Carom), 129.3 (O, Carom), 129.1 (1, 2C, Carom), 128.4 (1, 2C, Carom), 126.9 (1, Carom), 98.9 (O, C6), 81.5 (1, C10), 80.7 (1, C15), 73.2 (1, C13), 72.2 (1, C7), 70.8 (1, C2), 68.1 (1, br signal, C11), 57.1 (3, OMe), 48.0 (3, OMe), 45.2 (2, C18), 37.8 (O, C14), 35.0 (1, C3 or C4), 34.9 (1, C3 or C4), 32.1 (2, Se-CH₂), 31.0 (2, C5 or C12 or C16 or C17), 30.7 (2, C5 or C12 or C16 or C17), 30.5 (2, C5 or C12 or C16 or C17), 25.9 (3, 3C, ^tBu-Si), 25.8 (3, C14-Me), 25.5 (2, C5 or C12 or C16 or C17), 19.3 (3, br signal, C14-Me), 18.4 (3, C2-Me), 18.0 (O, C-Si), 4.2 (3, C3-Me), -4.4 (3, Me-Si), -5.1 (3, Me-Si); *m/z* (FAB, NaI) 878 (50), 876 [(M+Na)⁺, 100%], 874 (50), 720 (10), 718 (15), 439 (10), 413 (10); Found : (M+Na)⁺ 876.3152. C₄₂H₆₄O₈NCISiNa requires *M*, 876.3153.

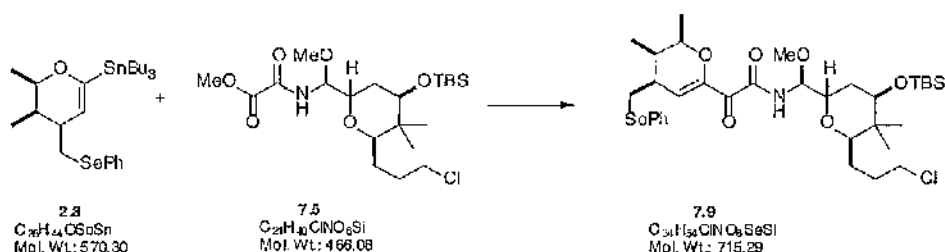
(*S*)-Benzoic acid ([[(2*S*,4*R*,6*R*)-4-(*tert*-butyldimethylsilyloxy)-6-(3-chloropropyl)-5,5-dimethyl-tetrahydro-pyran-2-yl]-(*R*)-methoxy-methyl]-carbamoyl)-((2*R*,4*R*,5*R*,6*R*)-2-methoxy-5,6-dimethyl-4-phenylsilylmethyl-tetrahydro-pyran-2-yl)-methyl ester (7.8b)



mp 92-94°C (hexanes/Et₂O); $[\alpha]_D^{20} +56.0$ (c 0.3, CHCl₃); ν_{\max} film/cm⁻¹ 3431, 3358, 3070, 2955, 2930, 2856, 1729, 1697, 1508, 1473, 1451, 1270, 1071; δ_H (400 MHz, CDCl₃): 8.11 (2H, dd, *J* 8.5, 1.3, Harom), 7.62 (1H, tt, *J* 7.5, 1.0, Harom), 7.51-7.46 (4H, m, Harom), 7.29-7.24 (3H, m, Harom), 7.14 (1H, d, *J* 9.6, NH), 5.73 (1H, s, C7-H), 5.16 (1H, dd, *J* 9.6, 3.3, C10-H), 3.86 (1H, dq, *J* 6.5, 2.0, C2-H), 3.72 (1H, app q, *J* 4.0, C11-H), 3.65 (1H, dd, *J* 5.6, 3.6, C13-H), 3.45 (3H, s, OMe), 3.41 (3H, s, OMe), 3.37 (1H, dd, *J* 11.4, 2.2, C15-H), 3.24 (1H, ddd, *J* 10.8, 7.5, 5.4, C18-H_AH_B), 3.15 (1H, dt, *J* 10.7, 6.0, C18-H_AH_B), 2.87 (1H,

dd, J 11.9, 8.0, Se-CH_AH_B), 2.83 (1H, dd, J 12.1, 7.2, Se-CH_AH_B), 2.39-2.23 (2H, m), 2.10-1.93 (3H, m), 1.87-1.42 (5H, m), 1.04 (3H, d, J 6.5, C2-Me), 0.98 (3H, s, C14-Me), 0.88 (9H, s, ^tBu-Si), 0.83 (3H, s, C14-Me), 0.70 (3H, d, J 6.9, C3-Me), 0.03 (3H, s, Si-Me), 0.02 (3H, s, Si-Me); δ_C (100 MHz, CDCl₃): 166.9 (0), 164.8 (0), 133.6 (1, Carom), 132.7 (1, 2C, Carom), 130.3 (0, Carom), 129.9 (1, 2C, Carom), 129.2 (0, Carom), 129.1 (1, 2C, Carom), 128.6 (1, 2C, Carom), 126.9 (1, Carom), 98.9 (0, C6), 81.6 (1, C10), 80.7 (1, C15), 73.1 (1, C7), 72.9 (1, C13), 70.2 (1, C2), 68.3 (1, br signal, C11), 57.0 (3, OMe), 49.1 (3, OMe), 45.0 (2, C18), 37.8 (0, C14), 35.1 (1, C3 or C4), 34.9 (1, C3 or C4), 32.4 (2, Se-CH₂), 31.2 (2, C5 or C12 or C16 or C17), 30.1 (2, C5 or C12 or C16 or C17), 29.7 (2, C5 or C12 or C16 or C17), 25.8 (3, 3C, ^tBu-Si), 25.6 (3, C14-Me), 25.5 (2, C5 or C12 or C16 or C17), 19.5 (3, br signal, C14-Me), 18.1 (3, C2-Me), 17.9 (0, C-Si), 4.2 (3, C3-Me), -4.4 (3, Me-Si), -5.1 (3, Me-Si); m/z (FAB, NaI) 878 (60), 876 [(M+Na)⁺, 100%], 874 (50), 715 (15), 536 (10); Found: (M+Na)⁺ 876.3168. C₄₂H₆₄O₈NCISiSeSiNa requires M , 876.3153

N-{[(2*S*,4*R*,6*R*)-4-(*tert*-Butyldimethylsilyloxy)-6-(3-chloropropyl)-5,5-dimethyl-tetrahydro-pyran-2-yl]-(*S*)-methoxy-methyl}-2-((4*S*,5*R*,6*R*)-5,6-dimethyl-4-phenylselaunylmethyl-5,6-dihydro-4*H*-pyran-2-yl)-2-oxo-acetamide (7.9)



To a solution of stannane **2.3** (430 mg, 0.754 mmol) in THF (5 ml) at -80°C was added dropwise *n*-BuLi (330 μl , 0.754 mmol, 2.29 M solution in hexane) and the bright yellow solution stirred while maintaining the temperature in between -75 and -80°C for 15 min. TMEDA (114 μl , 0.754 mmol) was added and after 10 min at -80°C , a solution of ester **7.5** (135 mg, 0.290 mmol) in THF (2.5 ml) pre-cooled to -78°C , was quickly added using a wide bore cannula. The light yellow solution was allowed to gradually warm up to -40°C over 1 h and then poured into brine (5 ml) and extracted with CH₂Cl₂ (3 x 10 ml). The combined extracts were dried (Na₂SO₄) and concentrated *in vacuo* to give a yellow oil which was purified by chromatography (SiO₂, PhMe and then 0-30% Et₂O in hexanes) to give coupling product **7.9** (129 mg, 0.180 mmol, 62% based on the right half fragment **7.5**) as a colourless oil.

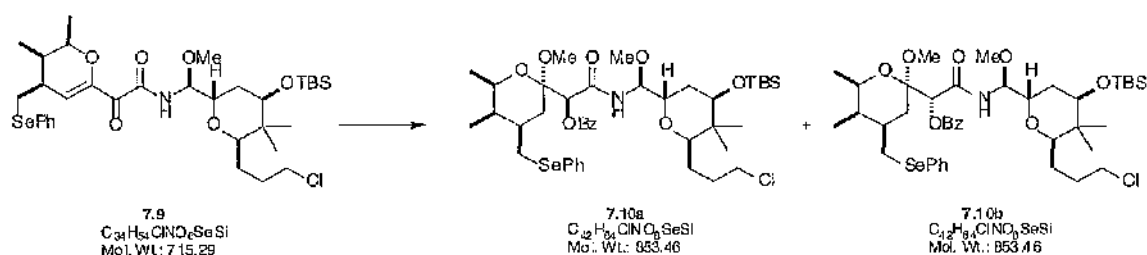
$[\alpha]_D^{23}$ -26.7 (c 0.75, CHCl₃); ν_{max} film/cm⁻¹ 3319, 2930, 2857, 1668, 1505, 1472, 1384, 1255, 1073; δ_H (400 MHz, CDCl₃): 7.49-7.45 (2H, m, Harom), 7.42 (1H, d, J 9.6, NH), 7.25-7.20 (3H, m, Harom), 7.05 (1H, br t, J 2.0, C5-H), 5.14 (1H, dd, J 9.8, 6.5, C10-H), 4.04 (1H, dq, J 6.5, 1.0, C2-H), 3.80 (1H, app q, J 5.6, C11-H), 3.50 (1H, dd, J 8.1, 3.9, C13-H), 3.47-3.37 (2H, m (7 lines), C18-H₂), 3.33 (3H, s, OMe), 3.14 (1H, d, J 9.7, C15-H), 2.93 (1H, d, J 14.0, Se-CH_AH_B), 2.91 (1H, d, J 13.8, Se-CH_AH_B), 2.84-2.77 (1H, m, C4-H), 2.00-1.93 (1H, m, C3-H), 1.86-1.77 and 1.65-1.45 (6H, 2 x m, C12-H₂, C16-H₂ and C17-H₂), 1.32 (3H, d, J 6.5, C2-Me), 0.89 (3H, s, C14-Me), 0.86 (9H, s, ^tBu-Si), 0.80 (3H, s, C14-Me), 0.76 (3H, d, J 7.0, C3-Me), 0.004 (3H, s, Me-Si), 0.000 (3H, s, Me-Si); δ_C (100 MHz, CDCl₃): 180.2 (0), 161.5 (0), 148.2 (0, C6), 133.0 (1, 2C, Carom), 129.2 (1, 2C, Carom), 129.2 (0, Carom), 127.3 (1, Carom), 124.2 (1, C5), 80.5 (1, C10), 79.8 (1, C15), 76.7 (1, C2), 72.7 (1, C13), 69.7 (1, C11), 56.6 (3, OMe), 45.4 (2, C18), 39.0 (1, C4), 38.4 (0, C14), 33.2 (1, C3), 30.7 (2, C12 or C16 or C17), 29.7 (2, C12 or C16 or C17), 29.5 (2, Se-CH₂), 26.0 (2, C12 or C16 or C17), 25.7 (3, 3C, ^tBu-Si), 24.7 (3, C14-Me), 18.1 (3, C2-Me), 18.0 (0, C-Si), 16.9 (3, C14-Me), 5.9 (3, C3-Me), -4.3 (3, Me-Si), -4.4 (3, Me-Si); m/z (FAB, NaI) 743 (5), 742 (10), 741 (20), 740

(50), 739 (45), 738 [(M+Na)⁺, 100%], 736 (50), 737 (25), 736 (55), 735 (20), 734 (15), 733 (5), 584 (4), 583 (6), 582 (18), 581 (16), 580 (32), 579 (2), 578 (2), 554 (20), 553 (10), 552 (40), 551 (10), 550 (25), 549 (10), 548 (10); *m/z* (FAB, NaI) 738 [(M+Na)⁺, 100%], 736 (50), 552 (40), 550 (10), 394 (30), 231 (90); Found : (M+Na)⁺ 738.2476. C₃₄H₅₄O₆SeSiClNa requires *M*, 738.2473.

(*S*)-Benzoic acid ([[(2*S*,4*R*,6*R*)-4-(*tert*-butyldimethylsilyloxy)-6-(3-chloropropyl)-5,5-dimethyl-tetrahydro-pyran-2-yl]-(*S*)-methoxy-methyl)-carbamoyl]-((2*R*,4*R*,5*R*,6*R*)-2-methoxy-5,6-dimethyl-4-phenylselanylmethyl-tetrahydro-pyran-2-yl)-methyl ester (7.10a)

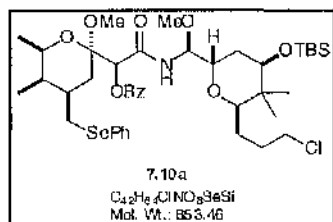
and

(*S*)-Benzoic acid ([[(2*S*,4*R*,6*R*)-4-(*tert*-butyldimethylsilyloxy)-6-(3-chloropropyl)-5,5-dimethyl-tetrahydro-pyran-2-yl]-(*S*)-methoxy-methyl)-carbamoyl]-((2*R*,4*R*,5*R*,6*R*)-2-methoxy-5,6-dimethyl-4-phenylselanylmethyl-tetrahydro-pyran-2-yl)-methyl ester (7.10b)



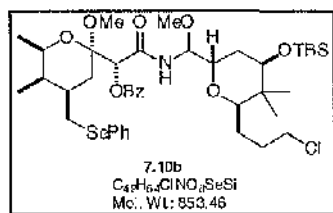
To a solution of acyl dihydropyran **7.9** (35 mg, 48.9 μ mol) in THF (3 ml) at -90°C was added LiBH(*s*-Bu)₃ (0.125 ml, 1.0 M solution in THF, 0.125 mmol) over 10 min. After 10 min maintaining the temperature between -80 and -85°C , the mixture was treated with brine (1 ml) and extracted with CH₂Cl₂ (3 x 5 ml). The combined organic extracts were dried (Na₂SO₄) and concentrated *in vacuo* to give the corresponding alcohols as a pale yellow oil. The crude alcohols were immediately dissolved in CH₂Cl₂ (2.5 ml) and MeOH (0.25 ml). Camphorsulfonic acid (4.0 mg, 17 μ mol) was added and the solution stirred at rt for 1 h before another batch of camphorsulfonic acid (4.0 mg, 0.017 mmol) was added. After 1.5 h at rt solid K₂CO₃ (16 mg, 0.11 mmol) was added slowly over 10 min. The reaction mixture was stirred for another 20 min and then poured onto saturated aqueous NaHCO₃ (2 ml) and extracted with CH₂Cl₂ (3 x 5 ml). The combined organic extracts were dried (Na₂SO₄) and concentrated *in vacuo*, to give the diastereoisomeric acetals as a pale yellow oil which were used immediately in the next step. A solution of benzoyl chloride (200 μ l, 1.71 mmol), DMAP (125 mg, 1.02 mmol), DIPEA (1.0 ml, 5.70 mmol) and 4Å MS (5) was prepared in CH₂Cl₂ (19 ml). To the crude acetal alcohols was added 2 ml of the above solution and the reaction mixture was stirred at rt for 15 h before MeOH was added (1 ml). After 20 min the mixture was poured into brine (2 ml) and extracted with CH₂Cl₂ (3 x 5 ml). The combined organic extracts were dried (Na₂SO₄) and concentrated *in vacuo*. The residue was purified by column chromatography (SiO₂, PhMe and then 0–30% Et₂O in hexanes) to give **7.10a** (25.1 mg, 29.4 μ mol, 60% over 3 steps) and **7.10b** (6.3 mg, 7.4 μ mol, 15%). The diastereomeric ratio between **7.10a** and **7.10b** is dr = 4:1).

(*S*)-Benzoic acid ([[(2*S*,4*R*,6*R*)-4-(*tert*-butyldimethylsilyloxy)-6-(3-chloropropyl)-5,5-dimethyl-tetrahydro-pyran-2-yl]-(*S*)-methoxy-methyl]-carbamoyl)-((2*R*,4*R*,5*R*,6*R*)-2-methoxy-5,6-dimethyl-4-phenylselanylmethyl-tetrahydro-pyran-2-yl)-methyl ester (7.10a)



$[\alpha]_D^{18} +60.0$ (c 1.2, CHCl_3); ν_{max} film/ cm^{-1} 3431, 3359, 3070, 2955, 2930, 2856, 1730, 1697, 1508, 1472, 1451, 1269, 1097, 1071; δ_{H} (400 MHz, CDCl_3): 8.08 (2H, dd, J 8.4, 1.3, Harom), 7.60 (1H, tt, J 7.5, 1.2, Harom), 7.52-7.44 (4H, m, Harom), 7.29-7.21 (3H, m, Harom), 6.81 (1H, d, J 9.6, NH), 5.57 (1H, s, C7-H), 5.26 (1H, dd, J 9.6, 5.6, C10-H), 3.93 (1H, dq, J 6.4, 2.1, C2-H), 3.81 (1H, app q, J 5.4, C11-H), 3.55-3.50 (3H, m, C13-H and C18-H₂), 3.42 (3H, s, OMe), 3.30 (1H, dd, J 10.5, 2.0, C15-H), 3.25 (3H, s, OMe), 2.92 (1H, dd, J 12.0, 6.5, Se-CH_AH_B), 2.84 (1H, dd, J 12.0, 9.3, Se-CH_AH_B), 2.38-2.27 (1H, m, C4-H), 2.00 (1H, dd, J 13.6, 3.6, C5-H_AH_B), 1.94-1.81 (3H, m), 1.72 (1H, t, J 13.3, C5-H_AH_B), 1.69-1.48 (4H, m), 1.17 (3H, d, J 6.6, C2-Me), 0.90 (9H, s, ^{*t*}Bu-Si), 0.822 (3H, s, C14-Me), 0.818 (3H, s, C14-Me), 0.77 (3H, d, J 7.0, C3-Me), 0.04 (6H, s, Si-Me₂); δ_{C} (100 MHz, CDCl_3): 167.6 (0), 165.2 (0), 133.5 (1, Carom), 132.5 (1, 2C, Carom), 130.3 (0, Carom), 130.0 (1, 2C, Carom), 129.1 (0, Carom), 129.0 (1, 2C, Carom), 128.5 (1, 2C, Carom), 126.8 (1, Carom), 98.6 (0, C6), 80.6 (1, C10), 79.7 (1, C15), 73.0 (1, C13), 72.7 (1, C7), 70.6 (1, C2), 69.9 (1, br signal, C11), 56.3 (3, OMe), 48.5 (3, OMe), 45.6 (2, C18), 38.2 (0, C14), 35.1 (1, C4), 34.9 (1, C3), 32.0 (2, Se-CH₂), 30.9 (2, C5), 30.8 (2, C12 or C16 or C17), 29.7 (2, C12 or C16 or C17), 26.1 (2, C12 or C16 or C17), 25.8 (3, 3C, ^{*t*}Bu-Si), 24.9 (3, C14-Me), 18.3 (3, C2-Me), 17.9 (0, C-Si), 17.2 (3, br signal, C14-Me), 4.3 (3, C3-Me), -4.5 (3, Me-Si), -5.0 (3, Me-Si); m/z (FAB, NaI) 878 (60), 876 [(M+Na)⁺, 100%], 874 (50), 792 (15), 790 (30), 788 (16), 660 (10), 658 (20), 656 (10), 538 (30), 536 (70), 534 (35); Found : (M+Na)⁺ 876.3155. C₄₂H₆₄O₈NCISeSiNa requires M , 876.3153

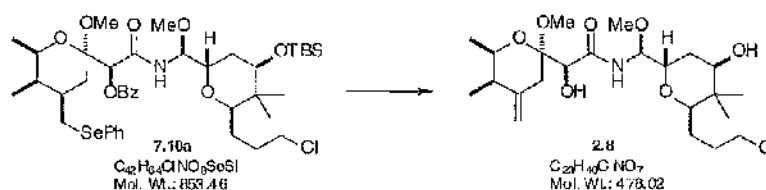
(*R*)-Benzoic acid ([[(2*S*,4*R*,6*R*)-4-(*tert*-butyldimethylsilyloxy)-6-(3-chloropropyl)-5,5-dimethyl-tetrahydro-pyran-2-yl]-(*S*)-methoxy-methyl]-carbamoyl)-((2*R*,4*R*,5*R*,6*R*)-2-methoxy-5,6-dimethyl-4-phenylselanylmethyl-tetrahydro-pyran-2-yl)-methyl ester (7.10b)



$[\alpha]_D^{20} +64.0$ (c 0.3, CHCl_3); ν_{max} film/ cm^{-1} 3431, 3358, 3070, 2955, 2930, 2856, 1729, 1697, 1508, 1473, 1451, 1270, 1071; δ_{H} (400 MHz, CDCl_3): 8.10 (2H, dd, J 7.2, 1.2, Harom), 7.61 (1H, tt, J 7.2, 1.2, Harom), 7.50-7.44 (4H, m, Harom), 7.27-7.23 (3H, m, Harom), 7.17 (1H, d, J 9.5, NH), 5.58 (1H, s, C7-H), 5.20 (1H, dd, J 9.5, 5.3, C10-H), 3.93 (1H, dq, J 6.5, 2.0, C2-H), 3.83-3.80 (1H, m, C11-H), 3.56-3.53 (3H, m, C13-H and C18-H₂), 3.43 (3H, s, OMe), 3.41 (3H, s, OMe), 3.29-3.22 (1H, d, J 9.9, C15-H), 2.87 (1H, dd, J 12.0, 8.2, Se-CH_AH_B), 2.83 (1H, dd, J 12.0, 7.3, Se-CH_AH_B), 2.32-2.23 (1H, m, C4-H), 2.02-1.80 (4H, m), 1.80-1.55 (5H, m), 1.11 (3H, d, J 6.5, C2-Me), 1.00 (3H, s, C14-Me), 0.91 (9H, s, ^{*t*}Bu-Si), 0.89 (3H, s,

C14-Me), 0.76 (3H, d, J 7.0, C3-Me), 0.04 (6H, s, Si-Me₂); δ_C (100 MHz, CDCl₃): 167.4 (O), 165.2 (O), 133.4 (1, Carom), 132.5 (1, 2C, Carom), 130.2 (O, Carom), 129.9 (1, 2C, Carom), 129.4 (O, Carom), 129.1 (1, 2C, Carom), 128.5 (1, 2C, Carom), 126.9 (1, Carom), 99.1 (O, C6), 80.7 (1, C10), 80.1 (1, C15), 73.6 (1, C7), 72.9 (1, C13), 70.6 (1, C2), 70.4 (1, br signal, C11), 56.8 (3, OMe), 49.5 (3, OMe), 45.7 (2, C18), 38.1 (O, C14), 35.1 (1, C3 or C4), 35.0 (1, C3 or C4), 32.2 (2, Se-CH₂), 31.1 (2, C5 or C12 or C16 or C17), 30.5 (2, C5 or C12 or C16 or C17), 29.9 (2, C5 or C12 or C16 or C17), 29.7 (2, C5 or C12 or C16 or C17), 25.8 (3, 4C, ^tBu-Si and C14-Me), 25.3 (3, C14-Me), 18.1 (3, C2-Me), 18.0 (O, C-Si), 4.2 (3, C3-Me), -4.5 (3, Me-Si), -5.0 (3, Me-Si); m/z (FAB, NaI) 878 (60), 876 [(M+Na)⁺, 100%], 874 (50), 792 (15), 790 (30), 788 (16), 660 (10), 658 (20), 656 (10), 538 (30), 536 (70), 534 (35); Found : (M+Na)⁺ 876.3159. C₄₂H₆₄O₈NCISiNa requires M , 876.3153

N-[[(*2S,4R,6R*)-6-(3-Chloropropyl)-4-hydroxy-5,5-dimethyl-tetrahydro-pyran-2-yl]-(*S*)-methoxy-methyl]-(*2S*)-2-hydroxy-2-[(*2S,5R,6R*)-2-methoxy-5,6-dimethyl-4-methylene-tetrahydro-pyran-2-yl]-acetamide (**2.8**)

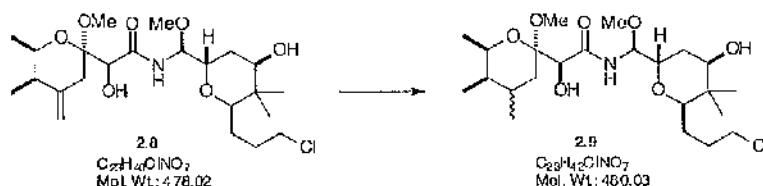


Sodium periodate (24 mg, 0.112 mmol) was added in one portion to a solution of the diastereoisomerically pure selenide **7.10a** (11 mg, 12.9 μmol) in MeOH/H₂O/CH₂Cl₂ (3:1:1, 3.5 ml). After 30 min the mixture was diluted with Et₂O (5 ml) and Et₃N (0.5 ml) and washed with H₂O (3 x 2 ml), dried (Na₂SO₄) and concentrated *in vacuo* to give the selenoxide as a colourless oil which was dissolved in toluene (2.4 ml) whereupon Et₃N (2.4 ml, 17.2 μmol) was added. After refluxing for 2 min, the bright yellow reaction mixture was poured into saturated aqueous NaHCO₃ (3 ml) and extracted with Et₂O (3 x 3 ml). The organic extracts were dried (Na₂SO₄) and concentrated *in vacuo* to give a pale yellow oil which was dissolved in MeOH (3 ml) to which was added aqueous LiOH (0.3 ml, 1.0 M, 0.3 mmol). After 30 min at rt the mixture was concentrated, the residue was dissolved in Et₂O (5 ml), washed with H₂O (2 x 2 ml) and brine (2 ml), dried (Na₂SO₄), and concentrated *in vacuo* to give a yellow oil which was used immediately in the next step. To a solution of the crude residue in THF (1 ml) was added TBAF·3H₂O (17 mg, 53.9 μmol) and 4Å MS (5). After 15 h at rt the reaction mixture was diluted with Et₂O (5 ml) and washed with saturated aqueous NaHCO₃ (3 ml). The aqueous phase was extracted with CH₂Cl₂ (3 x 3 ml) and the combined organic layers dried (Na₂SO₄) and concentrated *in vacuo* to give a yellow oil which was purified by column chromatography on silica gel (1 g) eluting with PhMe:hexanes:Et₂O:EtOAc:NEt₃ (100:0:0:0:1 then 0:100:0:0:1 → 0:0:100:0:1 → 0:0:50:50:1) to give C18-chloride-pederin-analogue **2.8** (4.1 mg, 8.58 μmol , 67% over 4 steps).

$[\alpha]_D^{18} +40$ (c 0.3, C₆D₆); ν_{max} film/cm⁻¹ 3477, 3392, 2935, 2367, 1685, 1500, 1114, 1092; δ_H (400 MHz, C₆D₆): 7.44 (1H, d, J 7.8, NH), 5.26 (1H, t, J 8.2, C10H), 4.77 (1H, t, J 1.9, =CH_AH_B), 4.71 (1H, t, J 2.0, =CH_AH_B), 4.03 (1H, s, C7H), 3.87-3.81 (2H, m, C2H and C11H), 3.60-3.53 (1H, m, C18-H_AH_B), 3.56 (3H, s, OMe), 3.24-3.16 (1H, m, C13H), 3.20 (3H, s, OMe), 2.82-2.73 (3H, m, C5-H_AH_B, C15H and C18-H_AH_B), 2.42 (1H, d, J 14.1, C₅-H_AH_B), 1.94 (1H, dq, J 7.0, 2.4, C3H), 1.86-1.67 (3H, m), 1.56-1.44 (1H, m), 1.32-1.22 (2H, m), 1.00 (3H, d, J 6.5, C2Me), 0.98 (3H, d, J 7.0, C3Me), 0.80 (3H, s, C14Me), 0.62 (3H, s, C14-Me), 0.20 (2H, br s, 2 x OH); δ_C (90 MHz, C₆D₆): 171.8 (O, C=O), 145.8 (O, C4), 108.5 (2, =CH₂),

98.2 (0, C6), 83.6 (1, C7), 78.9 (1, C10), 73.0 (1, C15), 72.3 (1, C2 or C11), 70.9 (1, C13), 68.0 (1, C2 or C11), 67.1 (2, C18), 55.5 (3, OMe), 47.7 (3, OMe), 40.6 (1, C3), 37.4 (0, C14), 33.4 (2, C5), 30.0 (2, C12 or C16 or C17), 24.3 (2, C12 or C16 or C17), 23.8 (2, C12 or C16 or C17), 20.9 (3, C14-Me), 16.6 (3, C2-Me), 10.6 (3, 2C, C3-Me and C14-Me); m/z (FAB mode) 464 [(M-HCl+Na)⁺, 100%]; Found: (M-HCl+Na)⁺, 464.2621. C₂₃H₃₉NO₇Na requires M , 464.2624.

N-{[(2*S*,4*R*,6*R*)-6-(3-Chloro-propyl)-4-hydroxy-5,5-dimethyl-tetrahydro-pyran-2-yl]-(*S*)-methoxy-methyl}-(*S*)-2-hydroxy-2-((2*S*,4*R*,5*R*,6*R*)-2-methoxy-4,5,6-trimethyl-tetrahydro-pyran-2-yl)-acetamide (2.9)



Adams catalyst (PtO₂·xH₂O, 4.0 mg) was added to a solution of olefin 2.8 (3.0 mg, 6.27 μmol) in freshly distilled benzene (3 ml). Gaseous hydrogen was bubbled into the solution for 5 min until giving a black suspension which was stirred under H₂ atmosphere at room temperature for 3 days. The reaction was monitored by ¹H NMR (360 Mhz, C₆D₆) spectroscopy by observing the disappearance and appearance of the following signals :

Disappearance of :

4.77 (1H, t, J 1.9, =CH_AH_B)

4.71 (1H, t, J 2.0, =CH_AH_B)

3.56 (3H, s, OMe)

3.20 (3H, s, OMe)

2.42 (1H, d, J 14.1, C₅-H_AH_B)

Appearance

3.58 (3H, s, OMe) of major diastereomer

3.23 (3H, s, OMe) of major diastereomer

3.57 (3H, s, OMe) of minor diastereomer

3.29 (3H, s, OMe) of minor diastereomer

After 3 d, the reaction mixture was filtered through celite and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (1 g) eluting with Et₂O:EtOAc (1:1) to give a mixture of the two diastereomers in the ratio 7:3 (3.0 mg, 6.25 μmol, 99%). The diastereomeric ratio was determined by integration of the signal derived from C7-II (III, s) at δ = 3.96 ppm (major) and 4.02 ppm (minor).

ν_{max} film/cm⁻¹ 3469, 3392, 2930, 1726, 1688, 1501, 1459, 1272, 1119, 1087, 582.

The ¹H NMR spectroscopic data is described below without the integration, or assignment using the abbreviations **Ma** for major diastereoisomer, **mi** for minor diastereoisomer.

δ_{H} (400 MHz, C₆D₆): 7.45 (d, J 7.6, NH, Ma+mi), 5.28-5.22 (m, C10H, Ma+mi), 4.30-4.16 (m), 4.02 (s, C7H, mi), 3.96 (s, C7H, Ma), 3.93-3.82 (m), 3.73-3.69 (m) 3.58 (3H, s, OMe, Ma), 3.57 (3H, s, OMe, mi), 3.29 (3H, s, OMe, mi), 3.23 (3H, s, OMe, Ma), 3.26-3.15 (m), 2.83-2.74 (m), 2.10-2.05 (app dd), 1.90-1.62 (m), 1.53-1.45 (m), 1.35-1.20 (m), 1.14 (app d, Me), 1.03 (app d, Me), 0.90 (app d, Me), 0.79 (app s, Me), 0.72 (app dd, mi), 0.61 (s, Me, Ma).

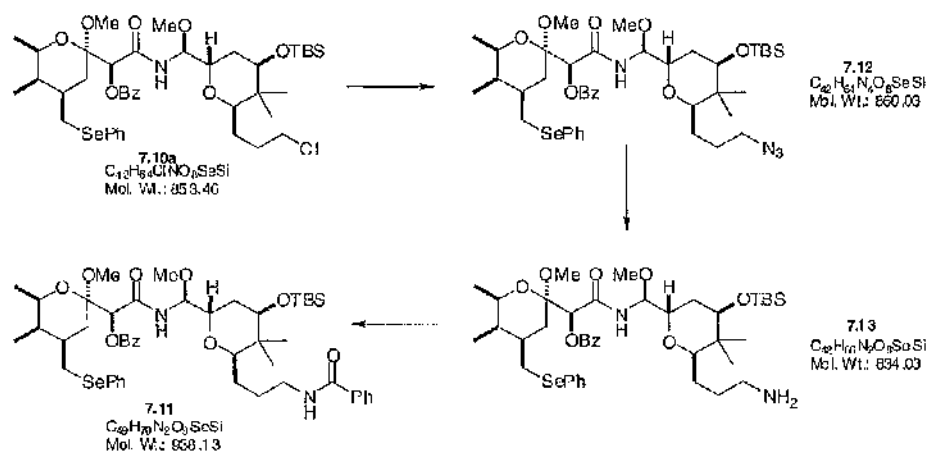
The ^{13}C NMR spectroscopy data is described below using the abbreviations **B** for big signals, **s** for small signals.

δ_{C} (90 MHz, C_6D_6): 172.00 (B), 166.23 (s), 98.29 (B), 97.57 (s), 84.31 (B), 84.37 (s), 78.92 (B), 78.86 (s), 73.00 (B), 73.0 (s), 72.33 (B), 72.28 (s), 70.90 (B), 69.11 (s), 66.99 (B), 66.95 (s), 66.68 (s), 62.61 (B), 55.58 (B), 55.49 (s), 47.07 (B), 47.61 (s), 37.43 (B), 37.84 (s), 36.46 (B), 36.00 (s), 31.67 (B), 31.10 (s), 30.01 (B), 30.01 (s), 29.46 (B), 29.11 (s), 29.04 (B), 28.87 (s), 28.34 (s), 27.94 (s), 24.33 (B), 24.30 (s), 23.86 (B), 22.79 (s), 22.00 (s), 20.84 (B), 19.78 (B), 18.02 (s), 17.19 (s), 17.09 (B), 14.16 (s), 12.92 (s), 11.81 (B), 10.57 (s), 9.81 (s)

m/z (FAB, NaI) 469 (10), 468 (15), 467 (25), 466 [(M-HCl+Na)⁺, 100%], 464 (8), 434 (10), 415 (5), 414 (27), 413 (100), 411 (5).

Found: (M-HCl+Na)⁺ 466.2782. $\text{C}_{23}\text{H}_{41}\text{NO}_7\text{Na}$ requires M , 466.2781.

(*S*)-Benzoic acid ([[(2*S*,4*R*,6*R*)-6-(3-benzoylpropyl)-4-(*tert*-butyldimethylsilyloxy)-5,5-dimethyl-tetrahydro-pyran-2-yl]-(*S*)-methoxy-methyl]-carbamoyl)-((2*R*,4*R*,5*R*,6*R*)-2-methoxy-5,6-dimethyl-4-phenylselanylmethyl-tetrahydro-pyran-2-yl)-methyl ester (7.11)



Formation of azide

Sodium azide (20 mg, 0.308 mmol) was added to the chloride 7.10a (23.0 mg, 26.9 μmol) in DMF (1 ml) and the mixture was refluxed for 2 min. Although the reaction could not be followed by TLC (azide product and starting chloride have the same r_f), the reaction mixture was concentrated *in vacuo* using a water bath at 50°C for 5 min and completion of the reaction was confirmed by ^1H NMR spectroscopy on the residue. The residue was then dissolved in CH_2Cl_2 (3 x 1 ml) and filtered through cotton plug. The filtrate was then concentrated *in vacuo* and the corresponding azide 7.12 was used immediately in the following step.

Reduction of azide to amine : 123

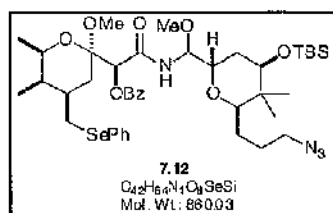
To the crude azide 7.12 in THF (0.5 ml) was added triphenylphosphine (40 mg, 0.153 mmol) at rt. After 12 h, water (0.05 ml, 2.8 mmol) was added and the reaction mixture was stirred at rt for another 18 h. The reaction mixture was then diluted with CH_2Cl_2 (3 ml), dried (Na_2SO_4) and then concentrated *in vacuo* to give the corresponding crude amine 7.13 as a pale yellow oil.

Acylation of the amine.

A solution of benzoyl chloride (30 μl , 0.26 mmol), pyridine (41 μl , 0.52 mmol) in CH_2Cl_2 (5 ml) at 0°C was prepared. To the crude amine 7.13, 0.5 ml of the above solution was added and the reaction mixture was

allowed to stir at 0°C for 3 h, before MeOH (0.5 ml) was added. After 10 min, PhMe (2 ml) was added and CH₂Cl₂ was removed by quick distillation *in vacuo*. The residue was purified by column chromatography (SiO₂, PhMe:hexanes:Et₂O:NEt₃ 100:0:0:1 → 0:100:0:1 → 0:50:50:1) to give benzamide **7.11** (19.7 mg, 0.021 mmol, 78% over 3 steps).

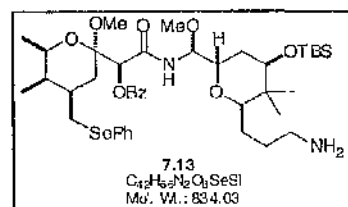
(S)-Benzoic acid ([[(2*S*,4*R*,6*R*)-6-(3-azidopropyl)-4-(*tert*-butyldimethylsilyloxy)-5,5-dimethyl-tetrahydro-pyran-2-yl]-(*S*)-methoxy-methyl]-carbamoyl)-((2*R*,4*R*,5*R*,6*R*)-2-methoxy-5,6-dimethyl-4-phenylselanylmethyl-tetrahydro-pyran-2-yl)-methyl ester (**7.12**)



¹H NMR and ¹³C NMR of the crude azide **7.12** still containing a little amount of DMF is reported here and structural assignments was deduced from the chloride **7.10a** assignments.

δ_{H} (360 MHz, CDCl₃): 8.08 (2H, dd, *J* 8.2, 1.1, Harom), 7.61 (1H, tt, *J* 7.3, 1.3, Harom), 7.51-7.45 (4H, m, Harom), 7.31-7.22 (3H, m, Harom), 6.81 (1H, d, *J* 9.7, NH), 5.56 (1H, s, C7-H), 5.25 (1H, dd, *J* 9.7, 5.1, C10-H), 3.92 (1H, dq, *J* 6.6, 2.1, C2-H), 3.84 (1H, app q, *J* 5.6, C11-H), 3.52 (1H, dd, *J* 7.4, 3.6, C13-H), 3.41 (3H, s, OMe), 3.30-3.23 (3H, m, C18-H₂ and C15-H), 3.25 (3H, s, OMe), 2.92 (1H, dd, *J* 12.2, 6.6, Se-CH_AH_B), 2.83 (1H, dd, *J* 12.1, 9.3, Se-CH_AH_B), 2.38-2.27 (1H, m, C4-H), 2.00 (1H, dd, *J* 13.5, 3.6, C5-H_AH_B), 1.87-1.39 (8H, m), 1.15 (3H, d, *J* 6.6, C2-Me), 0.90 (9H, s, ^tBu-Si), 0.81 (3H, s, C14-Me), 0.80 (3H, s, C14-Me), 0.76 (3H, d, *J* 7.0, C3-Me), 0.03 (6H, s, Si-Me₂); δ_{C} (100 MHz, CDCl₃): 167.6 (0), 165.2 (0), 133.5 (1, Carom), 132.5 (1, 2C, Carom), 131.5 (0, Carom), 130.3 (1, 2C, Carom), 129.2 (0, Carom), 129.1 (1, 2C, Carom), 128.5 (1, 2C, Carom), 126.8 (1, Carom), 98.8 (0, C6), 80.7 (1, C10), 79.9 (1, C15), 73.2 (1, C13), 72.7 (1, C7), 70.6 (1, C2), 69.7 (1, br signal, C11), 56.3 (3, OMe), 51.7 (2, C18), 48.5 (3, OMe), 38.2 (0, C14), 35.1 (1, C4), 34.9 (1, C3), 32.0 (2, Se-CH₂), 30.9 (2, C5), 30.8 (2, C12 or C16 or C17), 29.7 (2, C12 or C16 or C17), 26.1 (2, C12 or C16 or C17), 25.9 (3, C14-Me), 25.8 (3, 3C, ^tBu-Si), 18.3 (3, C2-Me), 17.9 (0, C-Si), 17.7 (3, C14-Me), 4.3 (3, C3-Me), -4.5 (3, Me-Si), -5.0 (3, Me-Si).

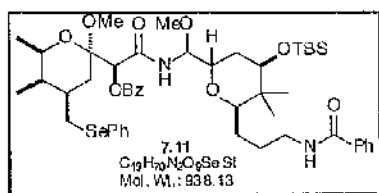
(S)-Benzoic acid ([[(2*S*,4*R*,6*R*)-6-(3-aminopropyl)-4-(*tert*-butyldimethylsilyloxy)-5,5-dimethyl-tetrahydro-pyran-2-yl]-(*S*)-methoxy-methyl]-carbamoyl)-((2*R*,4*R*,5*R*,6*R*)-2-methoxy-5,6-dimethyl-4-phenylselanylmethyl-tetrahydro-pyran-2-yl)-methyl ester (**7.13**)



Data of the amine were obtained on a previous experiment on a 26.9 μ mol scale of the chloride **7.10a**, from which the amine was isolated and purified by column chromatography (SiO₂, 0-25% MeOH in CH₂Cl₂) to give the amine (14 mg, 16.8 μ mol, 63%) as a colourless oil.

$[\alpha]_D^{19} +50.0$ (c 1.4, CHCl_3); ν_{max} film/ cm^{-1} 3350, 2955, 2925, 2854, 1729, 1697, 1508, 1460, 1270, 1094; δ_{H} (400 MHz, CDCl_3): 8.06 (2H, dd, J 8.4, 1.2, Harom), 7.60 (1H, t, J 7.4, 1.1, Harom), 7.52-7.44 (4H, m, Harom), 7.29-7.21 (3H, m, Harom), 7.01 (1H, br d, J 9.4, NH), 5.59 (1H, s, C7-H), 5.25 (1H, dd, J 9.5, 5.2, C10-H), 3.91 (1H, dq, J 6.6, 2.1, C2-H), 3.87 (1H, app q, J 5.0, C11-H), 3.52 (1H, dd, J 7.4, 3.6, C13-II), 3.45-3.39 (1H, m collapsed by OMe, C15-H or C18- $H_{\text{A}}H_{\text{B}}$), 3.43 (3H, s, OMe), 3.30-3.24 (2H, m), 3.27 (3H, s, OMe), 2.92 (1H, dd, J 12.0, 6.4, Se- $\text{CH}_A H_{\text{B}}$), 2.84 (1H, dd, J 12.0, 9.2, Se- $\text{CH}_A H_{\text{B}}$), 2.77-2.40 (2H, br signal, NH_2), 2.36-2.26 (1H, m, C4-H), 2.00 (1H, dd, J 13.7, 3.8, C5- $H_{\text{A}}H_{\text{B}}$), 1.90-1.35 (8H, m), 1.16 (3H, d, J 6.5, C2-Me), 0.90 (9H, s, $^t\text{Bu-Si}$), 0.83 (3H, s, C14-Me), 0.80 (3H, s, C14-Me), 0.76 (3H, d, J 7.0, C3-Me), 0.04 (6H, s, Si-Me₂); δ_{C} (100 MHz, CDCl_3): 167.8 (O), 165.2 (O), 133.6 (1, Carom), 132.5 (1, 2C, Carom), 130.4 (O, Carom), 130.0 (1, 2C, Carom), 129.1 (O, Carom), 129.0 (1, 2C, Carom), 128.6 (1, 2C, Carom), 126.8 (1, Carom), 98.9 (O, C6), 80.7 (1, C10), 80.4 (1, C15), 73.4 (1, C7), 72.8 (1, C13), 70.5 (1, C2), 69.6 (1, br signal, C11), 56.3 (3, OMe), 48.6 (3, OMe), 41.6 (2, C18), 38.2 (O, C14), 35.2 (1, C4), 34.9 (1, C3), 32.1 (2, Se- CH_2), 30.9 (2, C5), 30.8 (2, C12 or C16 or C17), 29.7 (2, C12 or C16 or C17), 29.3 (2, C12 or C16 or C17), 25.8 (3, 3C, $^t\text{Bu-Si}$), 22.7 (3, C14-Me), 18.4 (3, C2-Me), 18.0 (O, C-Si), 14.1 (3, C14-Me), 4.3 (3, C3-Me), -4.5 (3, Me-Si), -5.0 (3, Me-Si); m/z (FAB mode) 835 [(M+H)⁺, 100%], 833 (60), 770 (50), 530 (20), 442; Found : (M+H)⁺ 835.3834. $\text{C}_{42}\text{H}_{67}\text{O}_8\text{N}_2\text{SiSe}$ requires M , 835.3832.

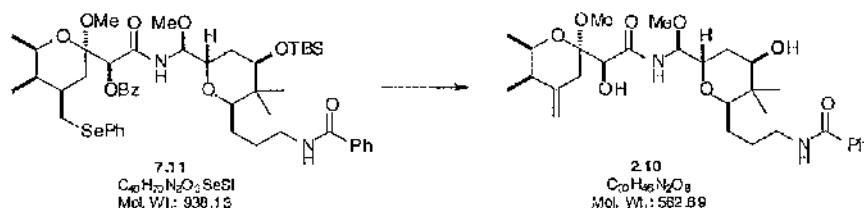
(*S*)-Benzoic acid ([[(2*S*,4*R*,6*R*)-6-(3-benzoylpropyl)-4-(*tert*-butyldimethylsilyloxy)-5,5-dimethyl-tetrahydro-pyran-2-yl]-(*S*)-methoxy-methyl]-carbamoyl)-((2*R*,4*R*,5*R*,6*R*)-2-methoxy-5,6-dimethyl-4-phenylselanyl-methyl-tetrahydro-pyran-2-yl)-methyl ester (7.11)



$[\alpha]_D^{23} +64.0$ (c 0.5, CHCl_3); ν_{max} film/ cm^{-1} 3368, 2955, 2929, 2856, 1735, 1726, 1701, 1696, 1686, 1655, 1648, 1508, 1500, 1490, 1476, 1466, 1459, 1450, 1438, 1271, 1096, 1072, 585, 576; δ_{H} (400 MHz, CDCl_3): 8.03 (2H, dd, J 7.2, 1.1, Harom), 7.84 (2H, dd, J 7.1, 1.3, Harom), 7.60 (1H, t, J 7.4, Harom), 7.50-7.43 (5H, m, Harom), 7.39 (2H, t, J 7.3, Harom), 7.30-7.21 (3H, m, Harom), 6.88 (1H, t, J 4.4, C18-NH), 6.70 (1H, d, J 9.7, N9-H), 5.57 (1H, s, C7-H), 5.32 (1H, dd, J 9.6, 6.0, C10-H), 3.89 (1H, dq, J 7.0, 2.1, C2-II), 3.84 (1H, app q, J 5.0, C11-H), 3.52-3.26 (4H, m, C13-H, C15-H, C18-H₂), 3.41 (3H, s, OMe), 3.24 (3H, s, OMe), 2.87 (1H, dd, J 12.0, 6.8, Se- $\text{CH}_A H_{\text{B}}$), 2.81 (1H, dd, J 12.0, 9.0, Se- $\text{CH}_A H_{\text{B}}$), 2.34-2.25 (1H, m, C4-H), 2.00 (1H, dd, J 13.5, 3.6, C5- $H_{\text{A}}H_{\text{B}}$), 1.91-1.42 (8H, m, C3-H, C5- $H_{\text{A}}H_{\text{B}}$, C12-H₂, C16-H₂, C17-H₂), 1.15 (3H, d, J 6.6, C2-Me), 0.87 (9H, s, $^t\text{Bu-Si}$), 0.82 (3H, s, C14-Me), 0.80 (3H, s, C14-Me), 0.74 (3H, d, J 7.0, C3-Me), 0.030 (3H, s, Si-Me), 0.028 (3H, s, Si-Me); δ_{C} (90 MHz, CDCl_3): 167.7 (O), 167.4 (O), 165.3 (O), 134.9 (O, Carom), 133.8 (1, Carom), 132.5 (1, 2C, Carom), 131.0 (1, Carom), 130.3 (O, Carom), 129.9 (1, 2C, Carom), 129.0 (O, 2C, Carom), 128.8 (O, Carom), 128.6 (1, 2C, Carom), 128.3 (1, 2C, Carom), 127.0 (1, 2C, Carom), 126.8 (1, Carom), 98.8 (O, C6), 80.2 (1, 2C, br signal, C10 and C13 or C15), 73.8 (1, C7), 72.6 (1, C13 or C15), 70.6 (1, C2), 70.4 (1, br signal, C11), 56.3 (3, OMe), 48.7 (3, OMe), 40.1 (2, C18), 38.4 (O, C14), 35.2 (1, C4), 34.9 (1, C3), 32.0 (2, Se- CH_2), 31.0 (2, C5), 30.7 (2, C12 or C16 or C17), 26.4 (2, C12 or C16 or C17), 26.0 (2, C12 or C16 or C17), 25.7 (3, 3C, $^t\text{Bu-Si}$), 24.7 (3, br signal, C14-Me), 18.3 (3, C2-Me), 17.93 (3, C14-Me), 17.84 (O, C-Si), 4.2 (3, C3-Me), -4.5 (3, Me-Si), -5.0 (3, Me-Si); m/z (FAB, NaI) 965 (5), 964 (15), 963 (40), 962 (55), 961 [(M+Na)⁺, 100%], 960 (35), 959 (55), 958 (25), 957

(20), 804 (20), 803 (50), 802 (100); Found : $(M+Na)^+$ 961.3929. $C_{49}H_{70}O_9N_2SiSeNa$ requires M , 931.3920.

***N*-[3-((2*R*,4*R*,6*S*)-4-Hydroxy-6-{[(2*S*)-2-hydroxy-2-((2*R*,5*R*,6*R*)-2-methoxy-5,6-dimethyl-4-methylene-tetrahydro-pyran-2-yl)-acetylamino]-(*S*)-methoxy-methyl]-3,3-dimethyl-tetrahydro-pyran-2-yl)-propyl]-benzamide (2.10)**



Sodium periodate (20 mg, 0.96 mmol) was added in one portion to a solution of the diastereoisomerically pure selenide **7.11** (9 mg, 9.6 μ mol) in MeOH/H₂O/CH₂Cl₂ (3:1:1, 3 ml). After 30 min the mixture was diluted with Et₂O (5 ml) and Et₃N (0.5 ml) and washed with H₂O (3 x 2 ml), dried (Na₂SO₄) and concentrated *in vacuo* to give the selenoxide as a colourless oil which was dissolved in toluene (2 ml) whereupon Et₃N (2 ml, 14.3 μ mol) was added. After refluxing for 2 min, the bright yellow reaction mixture was poured into saturated aqueous NaHCO₃ (3 ml) and extracted with Et₂O (3 x 3 ml). The organic extracts were dried (Na₂SO₄) and concentrated *in vacuo* to give a pale yellow oil which was dissolved in MeOH (3 ml) to which was added aqueous LiOH (0.3 ml, 1.0 M, 0.3 mmol). After 30 min at rt the mixture was concentrated, the residue was dissolved in Et₂O (5 ml), washed with H₂O (2 x 2 ml) and brine (2 ml), dried (Na₂SO₄), and concentrated *in vacuo* to give a yellow oil which was used immediately in the next step. To a solution of the crude residue in THF (1 ml) was added TBAF·3H₂O (14 mg, 44.4 μ mol) and 4Å MS (4). After 4 h at rt the reaction mixture was diluted with Et₂O (5 ml) and washed with saturated aqueous NaHCO₃ (3 ml). The aqueous phase was extracted with CH₂Cl₂ (3 x 3 ml) and the combined organic layers dried (Na₂SO₄) and concentrated *in vacuo* to give a yellow oil which was purified by column chromatography on silica gel (1 g) eluting with CH₂Cl₂:MeOH:NEt₃ (100:0:1 → 95:5:1) to give C18-benzamide-pederin-analogue **2.10** (4.2 mg, 7.46 μ mol, 78% over 4 steps) as a white solid.

mp 61–63°C (hexanes/Et₂O); $[\alpha]_D^{21} +45.3$ (c 0.3, C₆D₆); ν_{\max} film/cm⁻¹ 3373, 2967, 2929, 1672, 1651, 1533, 1309, 1122, 1073, 1041, 715, 694, 576; δ_H (400 MHz, C₆D₆): 7.77–7.73 (2H, m, Harom), 7.34 (1H, d, J 9.7, N9-H), 7.05–7.02 (3H, m, Harom), 6.23 (1H, t, J 5.2, C18-NH), 5.52 (1H, dd, J 9.6, 8.0, C10-H), 4.73 (1H, t, J 1.7, =CH_AH_B), 4.68 (1H, t, J 1.8, =CH_AH_B), 4.28 (1H, s, C7-H), 3.83 (1H, J 6.5, 2.7, C2-H), 3.76 (1H, ddd, J 8.0, 6.0, 3.2, C11-H), 3.35 (1H, dd, J 10.4, 4.6, C13-H), 3.32–3.22 (3H, m, C18-H₂ and C15-H), 3.28 (3H, s, OMe), 3.12 (3H, s, OMe), 2.68 (1H, d, J 14.2, C5-H_AH_B), 2.56 (1H, dt, J 14.2, 1.8, C5-H_AH_B), 2.00 (1H, ddd, J 13.4, 4.3, 3.2, C12-H_AH_B), 1.90 (1H, dq, J 7.0, 2.6, C3-H), 1.87–1.82 (1H, m), 1.62 (1H, ddd, J 13.5, 10.5, 6.0, C12-H_AH_B), 1.52–1.45 (1H, m), 1.31–1.14 (4H, m), 0.915 (3H, d, J 7.0, C3-Me), 0.911 (3H, d, J 6.5, C2-Me), 0.81 (6H, s, C14-Me₂); δ_C (90 MHz, C₆D₆): 170.8 (0, C=O), 166.0 (0, C=O), 145.4 (0, C4), 134.2 (0, Carom), 131.1 (1, Carom), 131.0 (1, Carom), 130.4 (1, Carom), 129.8 (1, 2C, Carom), 108.9 (2, =CH₂), 99.0 (0, C6), 78.4 (1, C10 or C15), 78.3 (1, C15 or C10), 72.8 (1, C7), 71.4 (1, C11), 70.6 (1, C13), 68.2 (1, C2), 54.7 (3, OMe), 47.8 (3, OMe), 40.5 (1, C3), 39.3 (2, C18), 37.3 (0, C14), 33.4 (2, C5), 29.1 (2, C12 or C16 or C17), 25.9 (2, C12 or C16 or C17), 25.5 (2, C12 or C16 or C17), 22.1 (3, C2-Me or C3-Me), 16.6 (3, C2-Me or C3-Me), 12.6 (3, br signal, C14-Me), 10.8 (3, C14-Me); m/z (FAB, NaI) 585 [($M+Na$)⁺, 70%], 481 (15), 176 (50); Found: ($M+Na$)⁺, 585.3157. $C_{30}H_{46}N_2O_8Na$ requires M , 585.3152.

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